MAR 2 7 2000 H 03 - 29 - 70 DAC

IN THESENITED STATES PATENT AND TRADEMARK OFFICE

DAC / Petition

In Re:

US Patent No. 5,360,800

07 7415TO

Issued:

1 November 1994

Inventors:

Ian H. Coates, Peter C. North, and Alexander W. Oxford.

Assignee:

Glaxo Group Limited

For:

TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-1-ONE DERIVATIVES

Re:

Patent Term Extension for U.S. Patent No. 5,360,800

RECEIVED

Asst. Commissioner of Patents Box Patent Extension Washington DC 20231

APR U 3 2000

Sir:

OFFICE OF PETITIONS
DEPUTY A/C PATENTS

Transmitted herewith is an Application for Extension of a Patent Term under 35 U.S.C. 156 with regard to U.S. Patent No. 5,360,800.

The Commissioner of Patent and Trademarks is hereby authorized to charge deposit account number 07-1392 in the amount of \$1,120.00 for receiving and acting upon this application for extension of term. In the event the actual fees due in connection with Applicant's application for patent term extension differ from the amount specified above, the Commissioner is hereby authorized to credit any overpayment or charge any underpayment to Applicants' deposit account number 07-1392. Triplicate copies of this letter are enclosed.

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01 FU:111 1120.00 CH

Inquiries and correspondences relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.
Vice President and Assistant Secretary
Intellectual Property Counsel
Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
(919) 483-2723

Respectfully submitted,

Glaxo Wellcome Inc.

MARCA 27,2000

David J. Levy, Ph. D.

Vice President and Assistant Secretary

Intellectual Property Counsel

Glaxo Wellcome Inc.

Docket No. **CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)** Applicant(s): Coates, et al. NDA 21-107 Serial No. Filing Date Examiner **Group Art Unit** Pat. No. 5,360,800 Granted: Nov 1, 1994 Invention: TETRAHYDRO-1H-PYRIDO [4,3-b] INDOL-1-ONE DERIVATIVES MAR 2 7 2000 Patent Term Extension for US Patent No. 5,360,800 (Identify type of correspondence) is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on March 27 2000 (Date) Rosalie M. Germano (Typed or Printed Name of Person Mailing Correspondence) (Signature of Person Mailing Correspondence) EM484297842US ("Express Mail" Mailing Label Number)

Note: Each paper must have its own certificate of mailing.

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Re:

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APH U 3 2000

Sir:

OFFICE OF PETITIONS DEPUTY A/C PATENTS

Applicant, Glaxo Wellcome Inc., a corporation of the State of North Carolina, represents that it is the Agent of Glaxo Group Limited, a corporation incorporated in England, for the purposes of filing an Application for Patent Term Extension for U.S. Patent No. 5,360,800 pursuant to the attached Declaration of David J. Levy and the Power of Attorney provided at EXHIBIT 1.

Applicant further represents, pursuant to 35 U.S.C. 156(d)(1), that Glaxo Group Limited, is the record owner and assignee of the entire right title and interest in and to Letters Patent of the United States of America No. 5,360,800 granted to Ian H. Coates, Peter C. North, and Alexander W. Oxford on 1 November 1994 for TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-1-ONE DERIVATIVES by virtue of an assignment to Glaxo Group Limited dated 22 August 1988, which assignment was recorded in the United States Patent and Trademark Office on 15 September 1988 on Reel 4993, Frame 0723. See EXHIBIT 2.

Applicants further represent, pursuant to 37 C.F.R. 1.785(d), that Applicant is the holder of the regulatory approval granted by the Food and Drug Administration ("FDA") for LOTRONEX® (Alosetron hydrochloride) Tablets (hereinafter, "LOTRONEX®"). A copy of the Food and Drug Administration (FDA) Approval Letter for LOTRONEX® is attached hereto as EXHIBIT 3.

Applicant hereby submits this Application for Extension of Patent Term under 35 U.S.C. 156 by providing the following information pursuant to 37 C.F.R. 1.740. For convenience, the information contained in this application will be presented according to the format set forth in 37 C.F.R. 1.740(a).

(1) This application for patent term extension is based upon the regulatory review period before the FDA, of Applicant's approved product, LOTRONEX® (alosetron hydrochloride) Tablets. The only active ingredient in LOTRONEX® Tablets is alosetron hydrochloride. A copy of the package insert approved by the FDA as part of New Drug Application 21-107 (NDA) is attached hereto as EXHIBIT 4. Identification of the approved product is provided as follows:

Chemical Name(s): 2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)-

methyl]-1H-pyrido[4,3-b]indol-1-one, hydrochloride

Molecular formula: C₁₇H₁₈N₄O·HCl

Structural formula:

Molecular weight:

330.8

Physical Form:

White to beige solid

- (2) The approved product, LOTRONEX® (Alosetron hydrochloride) Tablets was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, section 505 (21 U.S.C. 355). See EXHIBIT 3.
- (3) LOTRONEX[®] Tablets received permission for commercial marketing and use under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on <u>9 February 2000</u>. See EXHIBIT 3.
- (4) Alosetron hydrochloride, the only active ingredient in LOTRONEX® Tablets has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.
- (5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60-day period, which will expire on 9 April 2000.

(6) The complete identification of the patent for which extension of term is being sought is as follows:

U.S. Patent No.:

5,360,800

For:

TETROHYDRO-1H-PYRIDO[4,3-B]INDOL-1-ONE

DERIVATIVES

Inventors:

Ian H. Coates, Peter C. North, and Alexander W. Oxford

Assignee:

Glaxo Group Limited

Issued:

1 November 1994

Expiration Date:

2 February 2010

- (7) A complete copy of the patent identified in paragraph (6) above is attached hereto as EXHIBIT 5.
- (8) A copy of the Terminal Disclaimer filed for U.S. Patent 5,360,800, disclaiming the portion of patent term extending beyond the expiration date of U.S. Patent 5,183,820, is attached hereto as EXHIBIT 6.
 - (a) A copy of the Assignment filed in U.S. Patent 5,183,820, assigning all right, title and interest in U.S. Patent 5,183,820 to Glaxo Group Limited, is attached hereto as EXHIBIT 7.
 - (b) No certificates of correction have issued for this patent.
 - (c) Copies of all receipts of all maintenance fee payments made with respect to U.S. Patent 5,360,800 are attached hereto as EXHIBIT 8.
 - (d) No reexamination certificate exists in respect of U.S. Patent 5,360,800.

- (9) United States Patent 5,360,800 claims the active ingredient, alosetron hydrochloride, in the approved product LOTRONEX® Tablets. Applicant hereinbelow lists each applicable patent claim and demonstrates the manner in which each applicable claim reads on the approved product or method of using the approved product.
 - (a) Claim 1 reads as follows: "A compound of formula (I)

$$\bigcap_{\substack{N\\ | CH_2)_n}} \operatorname{Im}$$
 (I)

wherein Im represents an imidazolyl group of the formula:

$$\mathbb{N} \longrightarrow \mathbb{N} \mathbb{N}^3$$
 or $\mathbb{R}^3 \mathbb{N} \longrightarrow \mathbb{N}$

and R^1 represents a hydrogen atom or a group selected from C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, phenyl, phenyl C_{1-3} alkyl, phenylmethoxymethyl, phenoxymethyl, phenoxymethyl;

one of the groups represented by R², R³, and R⁴ is a hydrogen atom or a C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₆alkenyl, phenyl or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆alkyl group;

n represents 2 or 3;

or a physiologically acceptable salt or solvate thereof."

Claim 1 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where Im represents

$$\mathbb{N} \mathbb{N}^3$$

 R^1 is C_{1-6} alkyl, specifically C_1 alkyl or methyl; R^2 is a hydrogen atom; R^3 is a hydrogen atom; R^4 is C_{1-6} alkyl, specifically C_1 alkyl or methyl; and n is 2.

(b) Claim 2 reads as follows: "A compound according to claim 1 in which R¹ represents a C₁₋₄alkyl, C₃₋₄alkynyl, C₅₋₆cycloaklyl, C₅₋₆cycloaklylmethyl, phenylC₁₋₂alkyl, or phenylmethoxymethyl."

Claim 2 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R^1 is a C_{1-4} alkyl, namely C_1 alkyl or methyl.

(c) Claim 3 reads as follows: "A compound according to claim 1 in which R², R³, and R⁴ each independently represent a hydrogen atom or a C₁₋₃alkyl group."

Claim 3 reads on the approved product, LOTRONEX[®] Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R^2 is a hydrogen atom; R^3 is a hydrogen atom; and R^4 is a C_{1-3} alkyl group, specifically C_1 alkyl or methyl.

Claim 4 reads as follows: "A compound according to claim 1 in which R¹ represents a hydrogen atom or a C₁₋₄alkyl, C₃₋₄alkenyl, C₃₋₄alkynyl, C₅₋₆cycloalkyl, C₅₋₆cycloalkylmethyl, phenylC₁₋₂alkyl, or phenylmethoxymethyl; R² represents a hydrogen atom; and R³ and R⁴ each represent a hydrogen atom or a C₁₋₃alkyl group."

Claim 4 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R^1 is C_{1-4} alkyl, specifically C_1 alkyl or methyl; R^2 is a hydrogen atom; R^3 is a hydrogen atom; and R^4 is C_{1-3} alkyl, specifically C_1 alkyl or methyl.

(e) Claim 5 reads as follows: "A compound according to claim 1 in which R¹ represents a methyl, n-propyl, prop-2-ynyl, cyclopentyl, cyclopentylmethyl, or benzyl; R² and R³ each represent a hydrogen atom; and R⁴ represents a methyl group."

Claim 5 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula

I, where R^1 is methyl; R^2 and R^3 each represent a hydrogen atom; and R^4 is a methyl group.

(f) Claim 6 reads as follow: "A compound according to claim 4 in which n represents 2."

Claim 6 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R^1 is C_{1-4} alkyl, specifically C_1 alkyl or methyl; R^2 is a hydrogen atom; R^3 is a hydrogen atom; R^4 is C_{1-3} alkyl, specifically C_1 alkyl or methyl; and n represents 2.

(g) Claim 7 reads as follows: "A compound according to claim 5 in which n represents 2."

Claim 7 reads on the approved product, LOTRONEX[®] Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R¹ is methyl; R² and R³ each represent a hydrogen atom; R⁴ is a methyl group; and n represents 2.

(h) Claim 8 reads as follows: "2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one; or a physiologically acceptable salt or solvate thereof."

Claim 8 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of 2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one.

(i) Claim 10 reads as follows: "A compound according to claim 1 in the form of a hydrochloride, hydrobromide, sulphate, alkylsulphonate, arylsulphonate, phosphate, acetate, citrate, succinate, tartrate, fumarate or maleate salt."

Claim 10 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a hydrochloride salt form of the compound according to formula I of claim 1 (see item 9(a) supra).

(j) Claim 11 reads as follows: "The compound of claim 8 in the form of a hydrochloride salt."

Claim 11 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a hydrochloride salt of the compound according to claim 8 (see item 9(h) supra).

(k) Claim 13 reads as follows: "A pharmaceutical composition which comprises an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof together with at least one physiologically acceptable carrier or excipient."

Claim 13 reads on the approved product, LOTRONEX® Tablets, because the approved product is a pharmaceutical composition which contains the active ingredient alosetron hydrochloride, which is a compound according to claim 1 (see item 9(a) supra), together with lactose anhydrous, magnesium stearate, microcrystalline cellulose, and pregelatinized starch, which are pharmaceutically acceptable carriers.

(l) Claim 14 reads as follows: "A pharmaceutical composition according to claim 13 in a form adapted for oral or parenteral administration."

Claim 14 reads on the approved product, LOTRONEX® Tablets, because the approved product is a pharmaceutical composition according to claim 13 (see item 9(k) supra) which contains the active ingredient alosetron hydrochloride in a form adapted for oral administration.

(m) Claim 15 reads as follows: "A pharmaceutical composition according to claim 13 wherein the active ingredient is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof."

Claim 15 reads on the approved product LOTRONEX® Tablets, because the approved product is a pharmaceutical composition according to claim 13 (see item 9(k) supra) which contains the active ingredient alosetron hydrochloride, which is a physiologically acceptable salt, namely a hydrochloride salt, of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one.

(n) Claim 16 reads as follows: "A pharmaceutical composition according to claim 13, wherein the active ingredient is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl-1H-pyrido[4,3-b]indol-1-one hydrochloride."

Claim 16 reads on the approved product LOTRONEX® Tablets, because the approved product is a pharmaceutical composition according to claim 13 (see item 9(k) supra) containing the active ingredient alosetron hydrochloride, which is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

(o) Claim 17 reads as follows: "A method of treating a condition which is ameliorated by antagonism of 5HT₃ receptors which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof to relieve said condition."

Claim 17 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of a condition which is ameliorated by antagonism of 5HT₃ receptors, namely irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of a physiologically acceptable salt of a compound of formula (I) as defined in claim 1 (see item 9(a) supra).

(p) Claim 18 reads as follows: "A method according to claim 17 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof."

Claim 18 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of a condition which is ameliorated by antagonism of 5HT₃ receptors, namely irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of a physiologically acceptable salt of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one.

(q) Claim 19 reads as follows: "A method according to claim 17 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride."

Claim 19 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of a condition which is ameliorated by antagonism of 5HT₃ receptors, namely irritable bowel syndrome

in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

(r) Claim 27 reads as follows: "A method according to claim 17 for the treatment of irritable bowel syndrome."

Claim 27 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of irritable bowel syndrome, specifically treatment of irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of a physiologically acceptable salt of a compound of formula (I) as defined in claim 1 (see item 9(a) supra).

(s) Claim 28 reads as follows: "A method according to claim 27 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof."

Claim 28 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of irritable bowel syndrome, specifically treatment of irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of a physiologically acceptable salt, namely a hydrochloride salt, of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one.

(t) Claim 29 reads as follows: "A method according to claim 27 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride."

Claim 29 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of irritable bowel syndrome, specifically treatment of irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

(10) The relevant dates and information pursuant to 35 U.S.C 156(g) necessary to enable the Secretary of Health and Human Resources to determine the applicable regulatory review period are as follows:

(a) Effective Dates and Numbers of the INDs

The first Investigational New Drug Application ("IND") for alosetron hydrochloride became effective 10 May 1990; it was designated IND No. 34,672 (Alosetron Hydrochloride Tablets for Treatment of Cognition Disorders). See EXHIBIT 9A.

The second IND for alosetron hydrochloride became effective 11 April 1992; it was designated IND No. 39,083 (Alosetron Hydrochloride Tablets for Treatment of Schizophrenia). See EXHIBIT 9B.

The third IND for alosetron hydrochloride became effective 25 May 1994; it was designated IND No. 45,128 (Alosetron Hydrochloride for the Treatment of Carcinoid Diarrhea). See EXHIBIT 9C.

The fourth IND for alosetron hydrochloride became effective 6 September 1995; it was designated IND No. 48,487 (Alosetron Hydrochloride Tablets for Treatment of Irritable Bowel Syndrome). See EXHIBIT 9E.

The fifth IND for alosetron hydrochloride became effective 23 December 1999; it was designated IND No. 59,496 (Alosetron Hydrochloride Oral Solution). See EXHIBIT 9G.

Each of these IND's is discussed in more detail in Section 13, infra.

(b) Issue Date of Patent

US Patent No. 5,360,800 issued 1 November 1994 and claims a new drug, drug product, and methods of using the drug. See EXHIBIT 5.

(c) Submission Date and Number of NDA

The NDA for LOTRONEX® Tablets was submitted on 30 June 1999 and was designated NDA No. 21-107. See EXHIBIT 9F.

(d) Approval Date of NDA

NDA No. 21-107 for LOTRONEX® Tablets was approved by the FDA on 9 February 2000. See EXHIBIT 3.

- (11) A brief description of the significant activities undertaken by Applicant during both the IND and NDA regulatory periods is presented in a chronological form and is attached hereto as EXHIBIT 9 (including EXHIBITS 9-A through 9-G), "Due Diligence Log".
 - (a) The Due Diligence Log reflects significant communications with FDA during regulatory periods. Such communications include, but are not limited to: submission of preclinical reports; registration of clinical protocols and amendments thereof; registration of clinical investigators and amendments thereof; submission of adverse event reports; submission of IND Annual Reports, etc.
 - (b) Periods between such communications enumerated in the Due Diligence Log reflect Applicant's diligent undertaking of the necessary clinical studies and other activities required by the FDA in order to obtain approval for Applicant's product.

- (12) Applicant is of the opinion that U.S. Patent 5,360,800 is eligible for a 1076-day extension which is <u>not</u> subject to the 14-year limitation under 35 U.S.C. 156(c)(3). See EXHIBIT 10.
 - (a) Applicant has satisfied the eligibility criteria necessary to obtain a patent term extension pursuant to 35 U.S.C. 156.
 - (1) 35 U.S.C. 156(a)
 U.S. Patent No. 5,360,800 claims a drug product and a method of using a drug product.
 - (2) 35 U.S.C. 156(a)(1)

 The term of U.S. Patent No. 5,360,800 has not yet expired before submission of this application.
 - (3) 35 U.S.C. 156(a)(2)
 The term of U.S. Patent No. 5,360,800 has never been extended.
 - (4) 35 U.S.C. 156(a)(3)

 The application for extension is submitted by the agent for the owner of record in accordance with the requirements of 35 U.S.C. 156(d) and 37 C.F.R. 1.710 et seq.
 - (5) 35 U.S.C. 156(a)(4)
 The approved product, LOTRONEX® Tablets, has been subject to a regulatory review period before its commercial marketing or use.
 - (6) 35 U.S.C. 156(a)(5)(A)

 The commercial marketing or use of the approved product,

 LOTRONEX® Tablets, after the regulatory review period is the first
 permitted commercial marketing or use of the approved product under
 the provisions under which such regulatory review period occurred.
 - (b) Applicant herewith claims a patent term extension of 1076 days, which is not limited by the 14-year limitation under 35 U.S.C. 156(c)(3), for U.S. Patent No. 5,360,800 pursuant to U.S.C. 156(g) as follows:
 - (1) One half the IND regulatory review period for the approved product beginning 1 Nov 1994 (the IND period occurring after the date of issuance of U.S. Patent No. 5,360,800) and ending on 29 June 1999 (one day prior to the date on which the NDA for the approved product was initially submitted).

- (2) The full term of the NDA regulatory review period commencing 30 June 1999 (the date NDA 21-107 for the approved product was originally submitted) and ending on <u>9 February 2000</u> (the date on which NDA 21-107 was approved).
- (3) The sum of Items 12(b)(1) and 12(b)(2) supra is equal to $\underline{1076}$ days. See EXHIBIT 10.
- (c) Applicant herewith claims an extension expiry date of 13 January 2013 for U.S. Patent 5,360,800 pursuant to 35 U.S.C. 156(c)(3).
 - (1) The expiration of U.S. Patent 5,360,800, by virtue of the terminal disclaimer, is 2 February 2010.
 - (2) Extending the 2 February 2010 date by 1076 days would result in an expiration date of 13 January 2013. See EXHIBIT 10.
 - (3) 35 U.S.C. 156(c)(3) requires that term extensions if necessary be reduced in order to limit the expiration date of a patent receiving term extension to 14 years from the date of NDA approval. The expiration date of U.S. Patent 5,360,800 is therefore <u>not</u> limited by the provisions of 35 U.S.C. 156(c)(3). See EXHIBIT 10.

- (13) The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension. The following information is provided for consideration.
 - (a) Applicant filed the first IND for alosetron hydrochloride tablets on 10 April 1990 (for the treatment of cognition disorders); it was designated IND No. 34,672. IND No. 34,672 was received by the FDA on 10 April 1990. The effective date of IND No. 34,672 is therefore 10 May 1990, pursuant to 21 CFR 312.40(b). IND No. 34,672 was placed on clinical hold on 30 July 1991 by the Division of Neuropharmacological Drug Products. A request for inactive status for IND No. 34,672 was filed on 9 June 1994 and was acknowledged by the FDA on 9 July 1994. To Applicants' knowledge, IND No. 34,672 has not been terminated, and was pending as of the date of submission of NDA 21-107. See EXHIBIT 9A.
 - (b) Applicant filed the second IND for alosetron hydrochloride tablets on 11 March 1992 (for the treatment of schizophrenia); it was designated IND No. 39,083. IND No. 39,083 was received by the FDA on 12 March 1992. The effective date of IND No. 39,083 is therefore 11 April 1992, pursuant to 21 CFR 312.40(b). A request for inactive status for IND No. 39,083 was filed on 8 June 1994. To Applicants' knowledge, IND No. 39,083 has not been terminated, and was pending as of the date of the submission of NDA 21-107. See EXHIBIT 9B.
 - (c) The third IND for alosetron hydrochloride tablets -- IND No. 45,128 -- was filed on 22 April 1994, was received by FDA on 25 April 1994, and became effective 25 May 1994, pursuant to 21 CFR 312.40(b). See EXHIBIT 9C. The first U.S. studies of alosetron hydrochloride tablets for a gastrointestinal treatment use, namely for the treatment of carcinoid diarrhea, were conducted under IND No. 45,128. Specifically, the studies conducted under IND No. 45,128 were as follows: 1) An Effectiveness, Three Dose Study Of Alosetron In The Medium-Term Treatment Of Patients With Carcinoid Diarrhea, and 2) An Open-Label, Single Dose Trial Of Alosetron In The Treatment Of Patients With Carcinoid Diarrhea. Applicant contracted with Dr. Michael Camilleri, acting through the Mayo Foundation for Medical Education and Research ("Mayo"), to conduct these studies, and it was Dr. Camilleri who filed the IND.

Applicant collaborated closely on IND No. 45,128 and ultimately relied on the studies conducted under it in support of approval for NDA No. 21-107. Applicant's active role and deep vested interest in IND No. 45,128 are illustrated by the following:

- (i) <u>Full financial responsibility</u>: Applicant bore a contractual obligation to finance the studies conducted under IND No. 45,128, at considerable expense.
- (ii) <u>Supply of study drug</u>: Applicant manufactured and supplied all alosetron hydrochloride tablets administered to patients under IND No. 45,128.
- (iii) Substantiation and informational support of the IND filing:
 Applicant's earlier clinical and pre-clinical experience with alosetron hydrochloride tablets, as well as Applicant's information concerning chemistry, manufacturing, and controls, were indispensable elements of IND No. 45,128, without which studies could not have proceeded. IND No. 45,128 incorporated Applicant's earlier INDs for alosetron hydrochloride by reference (see below for more information about the earlier INDs), and otherwise relied extensively upon Applicant's previous drug development and manufacturing history with alosetron hydrochloride.
- (iv) Guidance and Technical Assistance in preparation of IND filing:
 Applicant provided guidance and technical assistance in meeting the
 FDA requirements in both the compilation of IND No. 45,128 and in
 meeting reporting obligations, as requested by Dr. Camilleri.
- (v) Rights to full use of study results: Applicant secured a contractual right to full use of the results of the studies conducted under IND No. 45,128. As provided by the governing contract, "GLAXO and MAYO agree that ... GLAXO shall have an exclusive License to use any and all [study] results in any way deemed by it to be necessary or advisable, either directly or through agents or otherwise, without payment of any compensation to MAYO for same."
- (vi) Rights to rely on study results in filings with FDA: Applicant secured a contractual right to rely on the results of the studies conducted under IND No. 45,128 to advance alosetron hydrochloride to approval. As provided by the governing contract, "MAYO agrees to approve GLAXO's reliance on such Study results in any future filings with the Food and Drug Administration ("FDA") for Alosetron."
- (vii) Rights to assistance in proceedings before FDA: Applicant secured a contractual right to assistance from Dr. Camilleri and Mayo in regulatory filings and proceedings, such as the filing of an NDA. As provided in the governing contract, "MAYO will make reasonable efforts to give GLAXO assistance and cooperation required by GLAXO related to the study in connection with informal presentations, discussions, submissions, administrative hearings or court proceedings involving the FDA or other federal or state agencies."
- (viii) Actual use and reliance on the study results in support of NDA 21-107:
 NDA 21-107 for Alosetron Hydrochloride Tablets refers to IND No.
 45,128 and reports data generated in the studies conducted by Dr.
 Camilleri. Moroever, Dr. Camilleri appeared on behalf of Applicant at

the meeting of the Gastrointestinal Drugs Advisory Committee on 16 November 1999, at which the panel reviewed NDA 21-107. At the meeting, Dr. Camilleri discussed data generated under IND No. 45,128. A transcript of Dr. Camilleri's remarks is attached as EXHIBIT 9D.

- (d) Applicant filed the fourth IND for alosetron hydrochloride tablets on 4 August 1995 (for the treatment of irritable bowel syndrome); it was designated IND No. 48,487. IND No. 48,487 was received by the FDA on 7 August 1995. The effective date of IND No. 48,487 is therefore 6 September 1995, pursuant to 21 CFR 312.40(b). Phase III clinical trials supporting approval of NDA No. 21-107 were conducted under IND No. 48,487. See EXHIBIT 9E.
- (e) Applicant filed a fifth IND for alosetron hydrochloride on 17 December 1999 (for Alosetron Hydrochloride Oral Solution); it was designated IND No. 59,496. The effective date of IND No. 59,496 was 23 December 1999, the FDA having waived the 30-day period under 21 CFR 312.40(b). See EXHIBIT 9G.
- (f) Applicants filed an NDA for LOTRONEX® (alosetron hydrochloride) Tablets on 30 June 1999; it was designated NDA No. 21-107. See EXHIBIT 9F. The NDA contains data from and references IND Nos. 34,672, 39,083, 45,128 and 48,487.
- (g) Applicants' NDA was approved on 9 February 2000. See EXHIBIT 3.
- (14) The Commissioner of Patent and Trademarks is hereby authorized to charge deposit account number <u>07-1392</u> in the amount of <u>\$1,120.00</u> for receiving and acting upon this application for extension of term. In the event the actual fees due in connection with Applicant's application for patent term extension differ from the amount specified above, the Commissioner is hereby authorized to credit any overpayment or charge any underpayment to Applicants' deposit account number 07-1392.
- (15) Inquiries and correspondences relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.
Vice President and Assistant Secretary
Intellectual Property Counsel
Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
(919) 483-2723

- (16) A duplicate of the application papers, certified as such, is attached hereto.
- (17) Submitted herewith is a Declaration by David J. Levy, Ph.D., Patent Counsel for Glaxo Wellcome Inc., which meets the criteria set forth in 37 CFR 1.740(b), and includes a Rule 3.73(b) certification on behalf of Glaxo Group Limited, which establishes the right of Glaxo Group Limited, as assignee, to take action in the Patent and Trademark Office in connection with this patent, including the naming of Applicant as its agent for purposes of filing this application, and grants power of attorney to the named registered patent attorneys.

The undersigned hereby certifies that this Application for Extension of Patent Term Under 35 U.S.C. 156, including Exhibits 1-10 and supporting papers, is being submitted as duplicate originals.

Respectfully submitted,

Glaxo Wellcome Inc.

3/27/2000

David J. Levy, Ph. D.

Vice President and Assistant Secretary

Intellectual Property Counsel

Glaxo Wellcome Inc.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

MAR 2 7 2000 In Re:

US Patent No. 5,360,800

Issued:

November 1, 1994

Inventors:

Ian H. Coates, Peter C. North, and Alexander W. Oxford.

Assignee:

Glaxo Group Limited

For:

TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-1-ONE DERIVATIVES

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Asst. Commissioner of Patents
Box Patent Extension
Washington, DC 20231

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DECLARATION OF DAVID J. LEVY, Ph.D. UNDER 37 C.F.R. 1.740(b)

CERTIFICATION UNDER 37 C.F.R. 3.73(b)

POWER OF ATTORNEY

DESIGNATION OF GLAXO WELLCOME INC. AS AGENT

Sir:

- I, David J. Levy, residing in Wake Forest, North Carolina, declare as follows:
- (1) I submit this declaration in connection with the Application for Patent Term Extension for US Patent No. 5,360,800 (hereinafter "Application"), which is submitted concurrently herewith.
- (2) Glaxo Group Limited has, by virtue of the Power of Attorney provided at EXHIBIT 1 of the Application, authorized me to perform acts in connection with letters patent and other Intellectual Property Rights.
- Pursuant to 37 C.F.R. § 3.73(b) and 35 U.S.C. § 156(d)(1), Glaxo Group Limited is the record owner and assignee of the entire right title and interest in and to US Patent No. 5,360,800 granted to Ian H. Coates, Peter C. North, and Alexander W. Oxford for TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-1-ONE DERIVATIVES by virtue of assignment to Glaxo Group Limited Recorded in the United States Patent and Trademark Office on 15 September 1988, Reel 4993, Frame 0723.

- (4) I have reviewed the evidentiary documents for the aforesaid chain of title and hereby certify pursuant to 37 C.F.R. § 3.73(b) that, to the best of my knowledge and belief, title is in the assignee, Glaxo Group Limited by virtue of the assignment noted in paragraph (3).
- (5) Glaxo Group Limited herein issues general authority to the following attorney(s) and/or agent(s), each of Glaxo Wellcome Inc., to prosecute this Application and transact all business in the US Patent and Trademark Office connected therewith.

Charles E. Dadswell	Reg. No. 35,851
Robert H. Brink	Reg. No. 36,094
Frank P. Grassler	Reg. No. 31,164
Lorie Ann Morgan	Reg. No. 38,181
James P. Riek	Reg. No. 39,009
Virginia C. Bennett	Reg. No. 37,092
Karen L. Prus	Reg. No. 39,337
Elizabeth Selby	Reg. No. 38,298
Christopher P. Rogers	Reg. No. 36,334
John Lemanowicz	Reg. No. 37,380
Bonnie Deppenbrock	Reg. No. 28,209

- Glaxo Group Limited does hereby make, constitute and appoint Glaxo Wellcome Inc. organized under the laws of North Carolina, having their principal place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709, United States of America as its special, true and lawful agent for the limited purpose of preparing and filing with the US Patent and Trademark Office an Application for Extension of Patent Term pursuant to 35 U.S.C. § 156(in respect of US Patent No. 5,360,800), and prosecuting said Application; and to do and perform each and every act in connection with the above-stated purpose which Glaxo Wellcome Inc. deems necessary or desirable.
- (7) I make this declaration pursuant to the attached Power of Attorney, having general authority to act on behalf of Glaxo Group Limited in patent matters, and as Vice President and Assistant Secretary, Intellectual Property Counsel for Glaxo Wellcome Inc., having general authority to act on behalf of Glaxo Wellcome Inc. in patent matters.
- (8) I am a patent attorney authorized to practice before the United States Patent and Trademark Office; my registration number is 27,655.
- (9) I have reviewed and understand the contents of the Application submitted herewith on behalf of Glaxo Wellcome Inc. (agent for Glaxo Group Limited), requesting a 1076-day extension of the term of US Patent No. 5,360,800.
- (10) I believe that US Patent No 5,360,800 is subject to extension pursuant to 37 C.F.R. §1.710.

- (11)I believe that a 1076-day extension of the term of US Patent No. 5,360,800 is justified under 35 U.S.C. §156 and the applicable regulations.
- (12)I believe that US Patent No. 5,360,800, for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 CFR 1.720.
- (13)Any inquiries and correspondence relating to this Application for Patent Term Extension of US Patent No. 5,360,800 are to be directed to:

David J. Levy, Ph.D. Vice President and Assistant Secretary Intellectual Property Counsel Glaxo Wellcome Inc. Five Moore Drive P.O. Box 13398 Research Triangle Park, NC 27709-3398 (919) 483-2723

fax: (919) 483-7988

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 5,360,800

David J. Levy, Ph.D.

Registration No. 27,655

Vice President and Assistant Secretary

Intellectual Property Counsel

Glaxo Wellcome Inc.

Five Moore Drive

Research Triangle Park, NC 27709

MARCH 27,2000

Date:



EXHIBIT 1

General Power of Attorney from Glaxo Group Limited to David J. Levy

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OFFICE OF PETITIONS DEPUTY A/C PATENTS

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POWER OF ATTORNEY

BY THIS POWER OF ATTORNEY given this day of June one thousand nine hundred and ninety seven GLAXO GROUP LIMITED a company incorporated in England (Registration No. 305979) and having its registered office at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN (hereinafter called "the Company"), HEREBY appoints Mr DAVID LEVY of Glaxo Wellcome Inc. five Moore Drive, P.O. Box 13398, Research Triangle Park, North Carolina 27709, USA to be its true and lawful agent and attorney (hereinafter called "the Attorney") on behalf and in the name of the Company or otherwise to do perform exercise or execute or concur with any other person or persons in doing performing or exercising in or for any country or countries or jurisdiction in any part of the world all or any of the following powers: acts, deeds and things in connection with letters patent, utility models, copyrights, trade mark registrations, trade marks, trade names, trade dress, logos, design rights, designs and all rights analogous thereto and all applications therefor and any other forms whatsoever of intellectual property rights, including know-how, all of which are hereinafter called "Intellectual Property Rights"; that is to say:

- In any country or countries or jurisdiction in any part of the world to make application or cause application to be made for the grant or issue or transfer to the Company or registration in its name of Intellectual Property Rights and to take all steps necessary for the same to be prosecuted, maintained, withdrawn, renewed, enforced, defended or extended
- 2. As the act and deed of the Company to sign, seal, deliver and execute all or any assignments or assurances to the Company of or under any Intellectual Property Rights or the right to and interest in any inventions to be the subject of Intellectual Property Rights for the purpose of fully and effectually vesting and transferring the same in and to the Company
- 3. As the act and deed of the Company to sign, seal, deliver and execute all or any assignments, assurances, licences or sub-licences from the Company of or under any Intellectual Property Rights or the right to and interest in any invention to be the subject of Intellectual Property Rights, for the purpose of fully and effectually vesting transferring or granting the same in and to any entity, whether in the United Kingdom or elsewhere, which is directly or indirectly owned or controlled by Glaxo Wellcome plc in so far as such documents can be executed without the Company's seal being affixed thereto.

For purposes of this Power of Attorney, the terms "entity" means, and includes, any person, firm or company or group of persons or unincorporated body; and "ownership" or "control" denotes the ownership or control of fifty per cent (50%) or more of the equity conferring voting rights and / or the ability otherwise to direct the business affairs of an entity.

- 4. To give undertakings or assurances to third parties and to any Trade Mark Registry or other official intellectual property agency or governmental department or otherwise responsible for the registration or protection of trade marks, trade names, trade dress, logos, design rights or designs for the purpose of best protecting or ensuring the co-existence of the Company's rights to trade marks, trade names, trade dress, logos, design rights or designs
- 5. To commence, prosecute and defend any proceedings or applications whether judicial or extra judicial relating to Intellectual Property Rights and to maintain, withdraw or settle the same
- 6. For and in connection with any Intellectual Property Rights to sign, seal, deliver and execute any power of attorney or other deed or document authorising any agent, including patent and trademark agents and attorneys, to act on behalf of the Company
- 7. To apply for the registration, amendment or cancellation of user rights in respect of any trade mark or trade name
- 8. To act in regard to all official communications which may now or hereafter be addressed to the Attorney relating to Intellectual Property Rights or the renewal thereof in such manner that the Attorney may be recognised as the authorised agent of the Company in all proceedings relating thereto
- 9. For all or any of the purposes contained herein as the act and deed of the Company to sign, seal, deliver, execute and do all such deeds, agreements, instruments and acts as shall be requisite or may be deemed proper for or in relation to the said purposes

AND THE COMPANY HEREBY RATIFIES and confirms and agrees to ratify and confirm all and_whatsoever the Attorney or any person, persons, firm or company appointed by them shall lawfully do or have done by virtue of the authorities herein contained

AND THE COMPANY HEREBY RATIFIES and confirms and agrees to ratify and confirm all and whatsoever the Attorney or any person, persons, firm or company appointed by them shall lawfully do or have done by virtue of the authorities herein contained

AND THE COMPANY HEREBY DECLARES that all instruments executed under and by virtue of this Power shall be as valid and effectual as if sealed by the Common Seal of the Company

AND THE COMPANY FURTHER DECLARES that this power is in substitution for and shall revoke all previous powers of attorney granted by the Company to the Attorney to do any of the acts and things hereby authorised to be done or remaining unrevoked: PROVIDED THAT nothing herein contained shall affect the validity of any act or thing done by the Attorney by virtue thereof before the execution of this power

IN WITNESS whereof GLAXO GROUP LIMITED has caused its Common Seal to be hereunto affixed the day and year first before written

The COMMON SEAL of)
GLAXO GROUP LIMITED)
was hereunto affixed)
in the presence of:)

DIRECTOR

Jeremy Strachan

DIRECTOR / SECRETARY / ASSISTANT SECRETARY
Simon Bicknell



EXHIBIT 2

Assignment to Glaxo Group Limited of Application for Letters Patent of United States Patent Application No. 07/239,626
U.S. Patent No. 5,360,800

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UNITED STATES DFPARTMENT OF COMMERCE Patent and Trade : Office

ASSISTANT SECRETARY AND COMMISSIONER OF PATENTS AND TRADEMARKS Washington, D.C. 20231

BACON & THOMAS TO: 625 SLATERS LA.. 4TH FLOOR ALEXANDRIA, VA 22314



UNITED STATES PATENT AND TRADEMARK OFFICE NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS - AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 COATES, IAN H. ASSIGNOR: 002 NORTH, PETER C. ASSIGNOR: 003 OXFORD, ALEXANDER W. DOC DATE: 08/22/88 DOC DATE: 08/22/88 DOC DATE: 08/22/88

RECORDATION DATE: 09/15/88 NUMBER OF PAGES 003 REEL/FRAME 4993/0723

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 GLAXO GROUP LIMITED, CLARGES HOUSE, 6/12 CLARGES ST., LON

DON, WIY 8DH, ENGLAND, A BRITISH CO.

SERIAL NUMBER 7-239626 FILING DATE 09/02/88 PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: LACTAM DERIVATIVES

- INVENTOR: OOI COATES, IAN H. INVENTOR: 002 NORTH, PETER C.

INVENTOR: 003 OXFORD, ALEXANDER W.

Ian Harold Coates, 20 Mandeville Road, Hertford, Hertfordshire, England.

Peter Charles North, 60 Downlands, Royston, Hertfordshire, SG8 5BY, England.

Alexander William Oxford, 60 Green Drift, Royston, Hertfordshire, England.

do hereby sell, assign, convey and set over to our assignees,

of, Glaxo Group Limited, a British Company, of Clarges House, 6/12 Clarges Street, London, W1Y 8DH, England.

our entire right, title and interest in and to an invention entitled.

Lactam Derivatives

and in and to the application for Letters Patent of the United States thereon, executed on even date herewith, and in and to any patent or patents that may issue on said application and invention in the United States of America and foreign countries, to assist in securing which we hereby covenant and agree on behalf of ourselves, our heirs, executors and legal representatives, to execute without further compensation all papers and assignment connected with such patent or application therefor, and we do hereby authorise and request the Commissioner of Patents to issue any patents maturing on said U.S. application to our assignee as the beneficial owner thereof; this assignment being executed on

IN WITNESS WHEREOF, we have hereunto set our hand and seal this 22nd day of August 1988

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COMMISSIONER OF PATENTS AND TRADEMARKS OFFICE lan Harold Coanes 1

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Peter Charles North

Alexander William Oxford

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"UNETED KINGDOM OF GREAT BRITAIN)
CICITY OF LONDON E N G L A N D) SS.

DE PINNA, SCORER

NOTARIES PUBLIC

3,ALBEMARLE STREET, LONDON W1X 3HF, TEL* 01-409 3188 TELEX: 8951242 FAX: 01-491 7302 Groups 2&3

15 RUE DE MARIGNAN. PARIS 75008 TEL: 43 59 2617 TELEX: 640383F 1, RICHARD GRAHAM ROSSER, of the City of London, Notary Public duly admitted and sworn practising in the said City,

DO HEREBY CERTIFY AND ATTEST:

THAT the signatures "Ian Harold Coates" "Peter Charles North" and "Alexander William Oxford" set and subscribed at foot of the hereunto annexed Assignment are in each case genuine, the same having been subscribed thereto by IAN HAROLD COATES, PETER CHARLES NORTH and ALEXANDER WILLIAM OXFORD, whose identities I attest.

IN TESTIMONY WHEREOF I have hereunto set my hand and affixed my Seal of Office in the City of London aforesaid, this twenty-fourth day of August One thousand nine hundred and eighty-eight.

1.00 to 1.11 \$4.00

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	(Hague Convention of 5 October 1961/Convention de La Haye du 5 octobre 1961)
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5.	6 the //e
7.	by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs/par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth
	en la companya de la
	F 040097
8.	Number/sous No F 049987
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	timbre:
	For the Secretary of State/Pour le Secrétaire d'Etat

IEEL 1,993 FAME 721

of, Glaxo Group Limited, a British Company, of Clarges House, 6/12 Clarges Street, London, W1Y 8DH, England.

our entire right, title and interest in and to an invention entitled.

Lactam Derivatives

and in and to the application for Letters Patent of the United States thereon, executed on even date herewith, and in and to any patent or patents that may issue on said application and invention in the United States of America and foreign countries, to assist in securing which we hereby covenant and agree on behalf of ourselves, our heirs, executors and legal representatives, to execute without further compensation all papers and assignment connected with such patent or application therefor, and we do hereby authorise and request the Commissioner of Patents to issue any patents maturing on said U.S. application to our assignment being executed on

IN WITNESS WHEREOF, we have hereunto set our hand and seal this 22nd day of August 1988

RECORDED
PATENT & TRADEMARK OFFICE

SEP 15 88

COMMISSIONER OF PATENTS AND TRADEMARKS OFFICE lan Harold Coances (1

Ian Harold Coates Charles Charles

(L.S)

Peter Charles North Nexande William Organ

Alexander William Oxford

(L.S)

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EXHIBIT 3

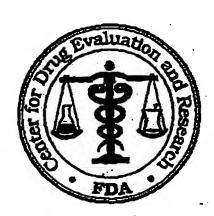
FDA Approval Letter for LOTRONEX® (Alosetron hydrochloride) Tablets NDA21-107

APP. U 3 2000

OFFICE OF PETITIONS
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Express Mail Label No. EM484297842US Food and Drug Administration
Division of Gastrointestinal and
Coagulation Drug Products
Document Control Room 6B-24
5600 Fisher's Lane
Rockville, MD 20857

Phone: 301-827-7310 Fax: 301-443-9285



Fax

To:	Mark Baumgartner	From: Paul E. Levine, Jr	<u>Jr</u>		
Fac	919-483-5063	Date: February 9, 2000			
Phone	919-486-3073	Pages: 4 (INCLUDING COVER PAGE)			
Re:	Approval Letter, NDA 21-107	CC:	· · · · ·		
□ Urge	ent 🗆 For Review 🗆 Please Co	mment X Please Reply 🗆 Please	Recycle		

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Comments: Please call to verify receipt of this fax

Please note that a copy of the approved labeling is not included in this fax. If a faxed copy is required, please notify me and one will be provided.

CONGRATULATIONS!



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration Rockville MD 20857

NDA 21-107

Glaxo Wellcome Inc.

Attention: Mark Baumgartner, RPh Product Director, Regulatory Affairs Five Moore Drive, P.O. Box 13398 Research Triangle Park, NC 27709

FEB 9 2000

Dear Mr. Baumgartner:

Please refer to your new drug application (NDA) dated June 29, 1999, received June 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex (alosetron hydrochloride) Tablets.

We acknowledge receipt of your submissions dated August 10, 20, 23, 25, 27, and 30; September 1, 2, 3, 10, 13, 14, 15, 17, 20, 21, 22, and 24; October 15, 25, 27, and 29; November 2, 12, 15, 19, and 30; December 1, 6, 7, and 22, 1999; and January 13, 17, and 21; February 7, and 8, 2000.

This new drug application provides for the use of Lotronex (alosetron hydrochloride) Tablets, 1 mg, for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea. The safety and effectiveness of Lotronex in mcn have not been established.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and patient package insert submitted February 8, 2000, immediate container and carton labels submitted December 6, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-107." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submissions dated December 22, 1999 and January 24, 2000. These commitments, along with any completion dates agreed upon, are listed below.

NDA 21-107 Page 2

Conduct the following studies:

- 1. A large, long-term (1 year) population risk trial to assess the incidence of colitis in patients receiving alosetron.
- 2. A study to assess efficacy and safety in men with Irritable Bowel Syndrome.
- 3. In vitro assessment of alosetron or metabolites on cultured endothelial cell integrity. One possible model could assess whether the drug or metabolites could affect extracellular matrix synthesis and/or could induce apoptosis of endothelial cells of restricted lineage.
- 4. Additional studies to clarify the metabolism and disposition of alosetron in vivo. Specific issues that should be addressed include the formation of n-desmethyl-alosetron and its metabolites, especially in Asians, and identification of the unidentified circulating metabolites from the mass balance study.
- 5. A pharmacokinetic study in subjects with hepatic impairment. In addition to alose tron kinetics, metabolite kinetic data should also be examined.
- 6. In vitro pharmacology, drug metabolism, and drug interaction studies. These should include 5HT₃ receptor affinities for any circulating or major metabolites (including conjugates), identification of P450 isozymes responsible for the formation of specific metabolites, plus the effect of alosetron and its metabolites on N-acetyltransferase 1 (NAT1), monoamine oxidases, and P450 isozymes, as appropriate.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to

NDA 21-107 Page 3

contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632)(21 CFR 314.55 (or 601.27)). FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations at this time since you have already indicated your intent, with your November 5 and December 20, 1999 Proposed Pediatric Study Requests, to pursue additional marketing exclusivity under the term of section 505A of FDAMA. These submissions are currently under review.

Submission of pediatric studies before you receive a Written Request may not fulfill the requirements for additional exclusivity. Please note that satisfaction of the requirements of 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40 Food and Drug Administration 5600 Fishers Lane Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

Vita F.C. Refueli 2/9/00

Victor F.C. Raczkowski, M.D., M.Sc. Deputy Director
Office of Drug Evaluation III

Center for Drug Evaluation and Research



EXHIBIT 4

Approved Product Information / Package Insert for LOTRONEX® (Alosetron hydrochloride) Tablets NDA 21-107

RECEIVED

APR U 3 2000

OFFICE OF PETITIONS DEPUTY A/C PATENTS

Express Mail Label No. EM484297842US

LOTRONEXTM

(alosetron hydrochloride)

Tablets

DESCRIPTION: The active ingredient in LOTRONEX Tablets is alosetron hydrochloride (HCl), a potent and selective antagonist of the serotonin 5-HT3 receptor type. Chemically, alosetron is designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b] indol-1-one, monohydrochloride. Alosetron is achiral and has the empirical formula: C₁₇H₁₈N₄O•HCl, representing a molecular weight of 330.8. Alosetron is a white to beige solid that has a solubility of 61 mg/mL in water, 42 mg/mL in 0.1M hydrochloric acid, 0.3 mg/mL in pH 6 phosphate buffer, and <0.1 mg/mL in pH 8 phosphate buffer. The chemical structure of alosetron is:

LOTRONEX Tablets for oral administration contain 1.124 mg alosetron HCl equivalent to 1 mg of alosetron. Each tablet also contains the inactive ingredients, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The blue film-coat contains hydroxypropyl methylcellulose, titanium dioxide, triacetin, and indigo carmine.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: *Mechanism of Action*: Alosetron is a potent and selective 5-HT3 receptor antagonist. 5-HT3 receptors are nonselective cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels and the resulting neuronal depolarization affect the regulation of visceral pain, colonic transit and gastrointestinal secretions.

• :

processes that relate to the pathophysiology of irritable bowel syndrome (IBS). 5-HT3 receptor antagonists such as alosetron inhibit activation of non-selective cation channels which results in the modulation of the enteric nervous system.

The cause of IBS is unknown. IBS is characterized by visceral hypersensitivity and hyperactivity of the gastrointestinal tract, which lead to abnormal sensations of pain and motor activity. Following distention of the rectum, IBS patients exhibit pain and discomfort at lower volumes than healthy volunteers. Following such distention, alosetron reduced pain and exaggerated motor responses, possibly due to blockade of 5HT₃-receptors.

In healthy volunteers and IBS patients, alosetron (2 mg orally, twice daily for 8 days) increased colonic transit time without affecting orocecal transit time. In healthy volunteers, alosetron also increased basal jejunal water and sodium absorption after a single 4-mg dose. In IBS patients, multiple oral doses of alosetron (4 mg twice daily for 6.5 days) significantly increased colonic compliance.

Single oral doses of alosetron administered to healthy men produced a dose-dependant reduction in the flare response seen after intradermal injection of serotonin. Urinary 6- β -hydroxycortisol excretion decreased by 52% in elderly subjects after 27.5 days of alosetron 2 mg orally twice daily. This decrease was not statistically significant. In another study utilizing alosetron 1 mg orally twice daily for 4 days, there was a significant decrease in urinary 6- β -hydroxycortisol excretion. However, there was no change in the ratio of 6- β -hydroxycortisol to cortisol, indicating a possible decrease in cortisol production. The clinical significance of these findings is unknown.

Pharmacokinetics: The pharmacokinetics of alosetron have been studied after single oral doses ranging from 0.05 mg to 16 mg in healthy men. The pharmacokinetics of alosetron have also been evaluated in healthy women and men and in patients with IBS after repeated oral doses ranging from 1 mg twice daily to 8 mg twice daily.

Absorption: Alosetron is rapidly absorbed after oral administration with a mean absolute bioavailability of approximately 50 to 60% (approximate range 30 to >90%). After administration of radiolabeled alosetron, only 1% of the dose was recovered in the feces as

unchanged drug. Following oral administration of a 1 mg alosetron dose to young men, a peak plasma concentration of approximately 5 ng/mL occurs at 1 hour. In young women, the mean peak plasma concentration is approximately 9 ng/mL, with a similar time to peak.

Food Effects: Alosetron absorption is decreased by approximately 25% by coadministration with food, with a mean delay in time to peak concentration of 15 minutes (see DOSAGE AND ADMINISTRATION).

Distribution: Alosetron demonstrates a volume of distribution of approximately 65 to 95 L. Plasma protein binding is 82% over a concentration range of 20 to 4000 ng/mL.

Metabolism and Elimination: Plasma concentrations of alosetron increase proportionately with increasing single oral doses up to 8 mg and more than proportionately at a single oral dose of 16 mg. Twice-daily oral dosing of alosetron does not result in accumulation. The terminal elimination half-life of alosetron is approximately 1.5 hours (plasma clearance is approximately 600 mL/min). Population pharmacokinetic analysis in IBS patients confirmed that alosetron clearance is minimally influenced by doses up to 8 mg.

Renal elimination of unchanged alosetron accounts for only 6% of the dose. Renal clearance is approximately 94 mL/min.

Alosetron is extensively metabolized in humans. The biological activity of these metabolites is unknown. A mass balance study was performed utilizing an orally administered dose of unlabeled and ¹⁴C-labeled alosetron. This study indicates that on a molar basis, alosetron metabolites reach additive peak plasma concentrations 9-fold greater than alosetron and that the additive metabolite AUCs are 13 fold greater than alosetron's AUC. Plasma radioactivity declined with a half-life two-fold longer than that of alosetron, indicating the presence of circulating metabolites. Approximately 73% of the radiolabeled dose was recovered in urine with another 24% of the dose recovered in feces. Only 7% of the dose was recovered as unchanged drug. At least 13 metabolites have been detected in urine. The predominant product in urine was a 6-hydroxy metabolite (15% of the dose). This metabolite was secondarily metabolized to a glucuronide that was also present in urine (14% of the dose). Smaller amounts of the 6-hydroxy metabolite and the 6-O-glucuronide also appear to be present in feces. A bis-oxidized dicarbonyl accounted for 14% of the dose and its monocarbonyl precursor accounted for another 4% in urine and 6% in feces. No other

urinary metabolite accounted for more than 4% of the dose. Glucuronide or sulfate conjugates of unchanged alosetron were not detected in urine.

In studies of Japanese men, an N-desmethyl metabolite was found circulating in plasma in all subjects and accounted for up to 30% of the dose in one subject when alosetron was administered with food. The clinical significance of this finding is unknown.

Alosetron is metabolized by human microsomal cytochrome P450 (CYP), shown in vitro to involve enzymes 2C9 (30%), 3A4 (18%), and 1A2 (10%). Non-CYP mediated Phase I metabolic conversion also contributes to an extent of about 11% (see PRECAUTIONS: Drug Interactions).

Population Subgroups:

Age: In some studies in healthy men or women, plasma concentrations were elevated by approximately 40% in individuals 65 years and older compared to young adults. However, this effect was not consistently observed in men (see PRECAUTIONS: Geriatric Use and DOSAGE AND ADMINISTRATION: Geriatric Patients).

Gender: Plasma concentrations are 30% to 50% lower and less variable in men compared to women given the same oral dose. Population pharmacokinetic analysis in IBS patients confirmed that alosetron concentrations were influenced by gender (27% lower in men).

Reduced Hepatic Function: No pharmacokinetic data are available in this patient group (see PRECAUTIONS: Hepatic Insufficiency and DOSAGE AND ADMINISTRATION: Patients with Hepatic Impairment).

Reduced Renal Function: Renal impairment (creatinine clearance 4 to 56 mL/min) has no effect on the renal elimination of alosetron due to the minor contribution of this pathway to elimination. The effect of renal impairment on metabolite kinetics and the effect of end-stage renal disease have not been assessed (see DOSAGE AND ADMINISTRATION: Patients with Renal Impairment).

CLINICAL TRIALS: Two 12-week treatment, multi-center, double-blind, placebo-controlled, dose-ranging studies were conducted to determine the dosage of oral LOTRONEX for subsequent evaluation in efficacy studies.

In women, of the doses studied, 1 mg of LOTRONEX twice daily was significantly more effective than placebo in providing relief of IBS pain and discomfort, decreasing the proportion of days with urgency, decreasing stool frequency, and producing firmer stools. Efficacy in men,, as assessed by producing adequate relief of IBS pain and discomfort, was not demonstrated at any dose of LOTRONEX.

The efficacy and safety of 1 mg of oral LOTRONEX twice daily for 12 weeks was studied in two US multi-center, double-blind, placebo-controlled trials of identical design (Studies 1 and 2) in non-constipated women with IBS meeting the Rome Criteria (see Appendix) for at least 6 months. For enrollment into the studies, patients were required to meet entry pain and stool consistency criteria. An average pain score of at least mild pain, as collected during a two-week screening period, was required. Women with severe pain were excluded. An entry stool consistency requirement was also incorporated to target women whose predominant bowel symptom was diarrhea or in which diarrhea was a prominent feature in their alternating pattern. Women with a history of severe constipation were excluded. Men were not studied.

The primary efficacy measure in these studies was the woman's weekly assessment of adequate relief of IBS pain and discomfort. Key secondary measures included percentage of days with urgency and daily assessment of stool frequency and consistency. Study 1 enrolled 647 women (71% diarrhea-predominant, 28% alternating between diarrhea and constipation, and 1% constipation-predominant) while Study 2 enrolled 626 women (71% diarrhea-predominant, 27% alternating between diarrhea and constipation, and 2% constipation-predominant). At entry into the studies, most women reported mild to moderate pain intensity and stool consistency of formed to loose.

In both trials, LOTRONEX 1 mg administered twice daily was significantly more effective than placebo in providing relief of IBS pain and discomfort.

In both Study 1 and Study 2, the beneficial effect on IBS pain and discomfort was demonstrated only in women with diarrhea-predominant IBS. Data in Figures 1 and 2 are presented for this subgroup. In Study 1, significantly more women reported relief of their abdominal pain and discomfort within 1 week of starting alosetron therapy than those who received placebo (Figure 1) start. In Study 2, this treatment effect was observed within

4 weeks (Figure 2). Once attained, significant treatment effect persisted throughout the remainder of the treatment period. Upon discontinuing LOTRONEX, symptoms returned. Within one week after discontinuing therapy, there was no difference between placebo and alosetron-treated women.

Figure 1: Percentage of Women (Diarrhea-Predominant)
Reporting Relief of IBS Pain and Discomfort in Study 1

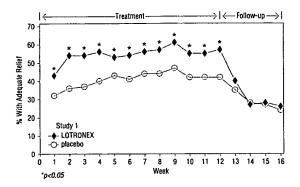
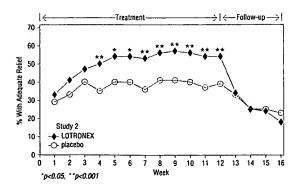


Figure 2: Percentage of Women (Diarrhea-Predominant)
Reporting Relief of IBS Pain and Discomfort in Study 2



In each study, women who received LOTRONEX reported a significant decrease in the percentage of days with urgency as compared to those who received placebo. Treatment with LOTRONEX also resulted in firmer stools and a significant decrease in stool frequency.

Significant improvement of these symptoms occurred within the first week of treatment and persisted throughout the 12 weeks of therapy. Upon discontinuance of treatment these symptoms returned. Within one week after discontinuing therapy, there was no difference between placebo and alosetron-treated patients. The efficacy of LOTRONEX for treatment longer than 12 weeks has not been established.

INDICATIONS AND USAGE: LOTRONEX is indicated for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea.

The safety and effectiveness of LOTRONEX in men have not been established.

CONTRAINDICATIONS: LOTRONEX is contraindicated in patients known to have hypersensitivity to any component of the product.

WARNINGS: Acute ischemic colitis was infrequently* reported in patients receiving LOTRONEX in 3-month clinical trials. The reported cases resolved over several days to weeks without sequelae or complications following supportive management. A causal association between treatment with LOTRONEX and acute colitis has not been established, nor have risk factors been identified. LOTRONEX should be discontinued in patients experiencing rectal bleeding and a sudden worsening of abdominal pain. These patients should be promptly evaluated and appropriate diagnostic testing considered

Constipation is a frequent and dose-related side effect of treatment with LOTRONEX. LOTRONEX should not be used in IBS patients who are currently constipated or whose predominant bowel symptom is constipation. In clinical studies, 25 to 30% of patients receiving alosetron experienced constipation. For the majority of these patients, constipation was mild to moderate in intensity and self-limited; however, approximately 9% of patients studied required interruption of treatment for a few days and approximately 10% could not tolerate twice daily dosing on a continuous basis and discontinued therapy. Patients

experiencing constipation who completed the 12-week treatment period had similar relief of abdominal pain as patients not experiencing constipation who completed the study.

Management of constipation with usual care including laxatives, fiber, or with a brief interruption of therapy may be considered. (See DOSAGE AND ADMINISTRATION)

*Infrequent is defined as occurring in 1/100 to 1/1000 patients.

PRECAUTIONS:

Information for Patients: See the tear-off leaflet at the end of the labeling for Information for the Patient.

Drug Interactions: In vitro human liver microsome studies and an in vivo metabolic probe study demonstrated that alosetron did not inhibit CYP enzymes 2D6, 3A4, 2C9, or 2C19. In vitro, at total drug concentrations 27-fold higher than peak plasma concentrations observed with the 1-mg dosage, alosetron inhibited CYP enzymes 1A2 (60%) and 2E1 (50%). In an in vivo metabolic probe study, alosetron did not inhibit CYP2E1 but did produce 30% inhibition of both CYP1A2 and N-acetyltransferase. Although not studied with alosetron, inhibition of N-acetyltransferase may have clinically relevant consequences for drugs such as isoniazid, procainamide, and hydralazine. The effect on CYP1A2 was explored further in a clinical interaction study with theophylline and no effect on metabolism was observed. Another study showed that alosetron had no clinically significant effect on plasma concentrations of the oral contraceptive agents ethinyl estradiol and levonorgestrel (CYP3A4 substrates). A clinical interaction study was also conducted with alosetron and the CYP3A4 substrate cisapride. No significant effects on cisapride metabolism or QT interval were noted. The effect of alosetron on monoamine oxidases and on intestinal first pass secondary to high intraluminal concentrations have not been examined. Based on the above data from in vitro and in vivo studies, it is unlikely that alosetron will inhibit the hepatic metabolic clearance of drugs metabolized by the major CYP enzyme 3A4, as well as the CYP enzymes 2D6, 2C9, 2C19, 2E1, or 1A2.

Alosetron does not appear to induce the major cytochrome P450 (CYP) drug metabolizing enzyme 3A. Alosetron also does not appear to induce CYP enzymes 2E1 or 2C19. It is not known whether alosetron might induce other enzymes.

Because alosetron is metabolized by a variety of hepatic CYP drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. The effect of induction or inhibition of individual pathways on metabolite kinetics and pharmacodynamic consequences has not been examined.

Hepatic Insufficiency: Due to the extensive hepatic metabolism and first pass metabolism of alosetron and metabolites, increased exposure to alosetron is likely to occur in patients with hepatic insufficiency.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In 2-year oral studies, alosetron was not carcinogenic in mice at doses up to 30 mg/kg/day or in rats at doses up to 40 mg/kg/day. These doses are, respectively, about 60 to 160 times the recommended human dose of alosetron of 2 mg/day (1 mg twice daily)based on body surface area. Alosetron was not genotoxic in the Ames tests, the mouse lymphoma cell (L5178Y/TK[±]) forward gene mutation test, the human lymphocyte chromosome aberration test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, or the in vivo rat micronucleus test for mutagenicity. Alosetron at oral doses up to 40 mg/kg/day (about 160 times the recommended daily human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male or female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 40 mg/kg/day (about 160 times the recommended human dose based on body surface area) and rabbits at oral doses up to 30 mg/kg/day (about 240 times the recommended daily human dose based on body surface area). These studies have revealed no evidence of impaired fertility or harm to the fetus due to alosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, LOTRONEX should be used during pregnancy only if clearly needed.

Nursing Mothers: Alosetron and/or metabolites of alosetron are excreted in the breast milk of lactating rats. It is not known whether alosetron is excreted in human milk. Because many

drugs are excreted in human milk, caution should be exercised when LOTRONEX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of all patients who received at least one dose of alosetron in premarketing studies, 211 were 65 years of age and over and 39 were 75 years of age and over. The safety profile of LOTRONEX was similar in older and younger patients.

In two placebo-controlled IBS safety and efficacy trials (Studies 1 and 2), 60 patients 65 years of age and over and 14 patients 75 years of age and over received 1-mg oral doses of LOTRONEX twice daily for up to 12 weeks. In both studies, subgroup analyses showed no evidence of differential treatment effects across the age categories assessed. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see CLINICAL PHARMACOLOGY: Population Subgroups: Age).

ADVERSE REACTIONS: In two large, placebo-controlled clinical trials conducted in the US (Studies 1 and 2), women (18 years of age and older) were treated with 1 mg of LOTRONEX twice-daily for up to 12 weeks. The adverse events in Table 1 were reported in 1% or more of patients who received LOTRONEX and occurred more frequently on LOTRONEX than on placebo: a statistically significant difference was observed for constipation in patients treated with LOTRONEX compared to placebo (p<0.0001).

Table 1: Adverse Events Reported in ≥1% of Female Patients and More Frequently on LOTRONEX 1 mg B.I.D. than Placebo (Studies 1 and 2)

	LOTRONEX	Placebo	
Body System	(N = 632)	(N = 637)	
Adverse Event			
Cardiovascular			
Hypertension	2%	<1%	
Ear, Nose, and Throat			
Allergic rhinitis	2%	<1%	
Throat and tonsil discomfort and pain	1%	<1%	
Bacterial ear, nose, and throat infections	1%	<1%	
Gastrointestinal			
Constipation	28%	5%	
Nausea	7%	6%	
Gastrointestinal discomfort and pain	5%	4%	
Abdominal discomfort and pain	5%	3%	
Gastrointestinal gaseous symptoms	3%	2%	
Viral gastrointestinal infections	3%	2%	
Dyspeptic symptoms	3%	1%	
Abdominal distention	2%	<1%	
Hemorrhoids	2%	<1%	
Neurology			
Sleep disorders	3%	2%	
Psychiatry			
Depressive disorders	2%	1%	

Gastrointestinal: The most frequent adverse event reported by patients treated with LOTRONEX was constipation (see WARNINGS). In clinical studies, constipation was reported in 25 to 30% of patients treated with LOTRONEX 1 mg twice daily for up to 12 weeks (n = 702). This effect was statistically significant compared to placebo (p<0.0001). Ten percent (10%) of patients treated with LOTRONEX withdrew from the studies due to constipation. Of the patients reporting constipation, 75% reported a single episode with the mean time to constipation onset of about 3 weeks. Occurrences of constipation were generally mild to moderate in intensity and transient in nature. Most constipation events resolved spontaneously with continued treatment. In studies 1 and 2, 9% of patients treated with LOTRONEX reported constipation and 4 consecutive days with no bowel movement; by protocol, therapy was withheld for 1 to 4 days. Following interruption of treatment, 88% of the affected patients resumed bowel movements within the 4-day period and were able to re-initiate treatment with LOTRONEX.

Hepatic: A similar incidence in elevation of ALT (>3-fold) was seen in patients receiving LOTRONEX or placebo (0.5% vs 0.4%) in studies of 12 weeks' and 12 months' duration. A single case of hepatitis (elevated ALT, AST, alkaline phosphatase, and bilirubin) without jaundice was reported in a 12-week study. A causal association with LOTRONEX has not been established.

Long-Term Safety: The pattern and frequency of adverse events in a long-term, placebocontrolled safety study in which women with IBS (n = 473) were treated with LOTRONEX 1 mg twice daily for up to 12 months were essentially the same as observed in 12-week safety and effectiveness trials. There were no reports of acute colitis in these alosetron-treated women.

Other Events Observed During the Premarketing Evaluation of LOTRONEX: During its premarketing assessment, multiple and single doses of LOTRONEX were administered resulting in 2574 patient exposures in 46 completed clinical studies. The conditions, dosages, and duration of exposure to LOTRONEX varied between trials, and the studies included healthy male and female volunteers as well as male and female patients with IBS.

In the listing that follows, reported adverse events were classified using a standardized coding dictionary. Only those events that an investigator believed were possibly related to

alosetron, occurred in at least 2 patients, and occurred at a greater frequency during treatment with LOTRONEX than during placebo administration are presented. Serious adverse events occurring in at least one patient for which an investigator believed there was reasonable possibility that the event was related to alosetron treatment and which occurred at a greater frequency in LOTRONEX than placebo-treated patients are also presented.

In the following listing, events are categorized by body system. Within each body system, events are presented in descending order of frequency. The following definitions are used: *Infrequent* adverse events are those occurring on one or more occasion in 1/100 to 1/1000 patients; *Rare* adverse events are those occurring on one or more occasion in fewer than 1/1000 patients.

Although the events reported occurred during treatment with LOTRONEX, they were not necessarily caused by it.

Cardiovascular - Infrequent: Arrhythmias.

Drug Interaction, Overdose and Trauma - Rare: Contusions and hematomas.

Ear Nose, and Throat - Infrequent: Nasal signs and symptoms. *Rare:* Ear signs and symptoms.

Eyes - Rare: Photophobia.

Gastrointestinal -Infrequent: Ischemic colitis. Rare: proctitis.

Hepatobiliary Tract and Pancreas - Infrequent: Abnormal bilirubin levels.

Lower Respiratory - Infrequent: Breathing disorders. **Rare:** Cough.

Neurological - Rare: Sedation and abnormal dreams.

Non-site Specific - Rare: Allergies, allergic reactions, unusual odors and taste.

Psychiatry - Infrequent: Anxiety.

Reproduction - Infrequent: Menstrual disorders. **Rare:** Sexual function disorders.

Skin - Rare: Acne and folliculitis.

Urology - Rare: Urinary infections, polyuria, and diuresis.

DRUG ABUSE AND DEPENDENCE: LOTRONEX has no known potential for abuse or dependence.

OVERDOSAGE: There is no specific antidote for overdose of LOTRONEX. Patients should be managed with appropriate supportive therapy. Individual oral doses as large as 16 mg have been administered in clinical studies without significant adverse events. This dose is 8 times higher than the recommended total daily dose. Inhibition of the metabolic elimination and reduced first pass of other drugs might occur with overdoses of alosetron (see PRECAUTIONS: Drug Interactions). Single oral doses of LOTRONEX at 15 mg/kg in female mice and 60 mg/kg in female rats (30 and 240 times, respectively, the recommended human dose based on body surface area) were lethal. Symptoms of acute toxicity were labored respiration, subdued behavior, ataxia, tremors, and convulsions.

DOSAGE AND ADMINISTRATION:

Usual Dose in Adults: The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food. Individual patients who experience constipation may need to interrupt treatment (see WARNINGS and ADVERSE REACTIONS: Gastrointestinal).

Pediatric Patients: No studies have been conducted in patients less than 18 years of age (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: No dosage adjustment is recommended for elderly patients (65 years of age and older) (see CLINICAL PHARMACOLOGY: Population Subgroups: Age and PRECAUTIONS: Geriatric Use).

Patients with Renal Impairment: No dosage adjustment is recommended for patients with renal impairment (creatinine clearance 4 to 56 mL/min) (see CLINICAL PHARMACOLOGY: Reduced Renal Function).

Patients with Hepatic Impairment: No studies have been conducted in patients with hepatic impairment (see PRECAUTIONS: Hepatic Insufficiency and CLINICAL PHARMACOLOGY: Population Subgroups: Reduced Hepatic Function).

HOW SUPPLIED: LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg alosetron), are blue, oval, film-coated tablets engraved with GX CT1 on one face in bottles

of 60 tablets (NDC 0173-0690-00) and 120 tablets (NDC 0173-0690-03) with child-resistant closures and Unit Dose Pack of 60 (NDC 0173-0690-04).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

APPENDIX

Diagnostic Criteria: Irritable Bowel Syndrome (IBS)*

At least three months continuous or recurrent symptoms of:

- 1. abdominal pain or discomfort which is:
 - (a) relieved with defecation,
 - (b) and/or associated with a change in frequency of stool,
 - (c) and/or associated with a change in consistency of stool;

and

- 1. two or more of the following, at least a quarter of occasions or days;
 - (a) altered stool frequency,
 - (b) altered stool form (lumpy/hard or loose/watery stool),
 - (c) altered stool passage (straining, urgency, or feeling of incomplete evacuation),
 - (d) passage of mucus,
 - (e) bloating or feeling of abdominal distention

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

US Patent No. 5,360,800

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Date of Issue: February 2000 RL-XXX

^{*}Thompson WG, Creed F. Drossman DA, et al. Functional bowel disease and functional abdominal pain, Gastroenterol Int 1992; 5: 75-91.

PHARMACIST--DETACH HERE AND GIVE LEAFLET TO PATIENT.

Information for the Patient

LOTRONEX™ (alosetron hydrochloride) Tablets

Read this information carefully before you start taking LOTRONEX (pronounced LOW-trah-nex) Tablets. Read the information included with LOTRONEX each time you refill your prescription, in case something has changed. This information does not take the place of discussions with your doctor.

What is LOTRONEX?

LOTRONEX is a prescription medicine used to treat irritable bowel syndrome (IBS) in women who have diarrhea as their main symptom. Lotronex has not been shown to work in men with IBS. IBS has been called by many names including irritable colon, and spastic colon. IBS is a medical condition causing cramping abdominal pain, abdominal discomfort, urgency (a sudden need to have a bowel movement), and irregular bowel habits such as diarrhea or constipation.

It is not clear why some people develop IBS. It may be caused by your body's overreaction to a body chemical called serotonin. This overreaction may cause your intestinal system to be overactive. LOTRONEX works by blocking the action of serotonin on the intestinal system. This reduces the cramping abdominal pain, abdominal discomfort, urgency, and diarrhea caused by IBS.

LOTRONEX may not work for every patient who takes it. For women who are helped by LOTRONEX, the medicine works faster in some and slower in others. Some women taking LOTRONEX will have relief from their IBS pain and discomfort within the first week of

use. Other women have relief of abdominal pain and discomfort within four weeks of starting LOTRONEX. Within one week, urgency and diarrhea occur less often for some patients. When you stop taking LOTRONEX, IBS symptoms will likely return within one week.

A. Who should not take LOTRONEX?

You should not start taking LOTRONEX when you are constipated or constipated most of the time.

Do not take LOTRONEX if you are allergic to LOTRONEX or any of its ingredients. The active ingredient in LOTRONEX is alosetron hydrochloride. The inactive ingredients are listed at the end of this leaflet.

Lotronex may not be right for you. Tell your doctor if you are:

- constipated most of the time.
- pregnant or plan to become pregnant.
- breast feeding.
- taking or planning to take any other medicines, including those you can get without a prescription.

B. How should LOTRONEX be taken?

Take LOTRONEX exactly as your doctor prescribes it. You can take Lotronex with or without food. If you miss a dose of LOTRONEX, do not double the next dose. Instead, simply go to the next regularly scheduled dosing time and take your normal prescribed dose of LOTRONEX

What are the possible side effects of LOTRONEX?

If you have a sudden worsening of abdominal pain or if you see blood in your stool (bowel

movement), call your doctor right away. These symptoms may be a sign of a serious

medical condition.

.. . . .

Constipation is a common side effect of treatment with LOTRONEX. If you become

constipated while taking LOTRONEX, call your doctor. Your doctor may tell you to stop

taking LOTRONEX or suggest other ways to manage your constipation.

This description of side effects is not complete. Your doctor or pharmacist can give you a

more complete list of side effects with LOTRONEX. Talk to your doctor right away about

any side effects you have.

Medicines are sometimes prescribed for purposes not listed in patient information leaflets.

Do not use Lotronex for a condition for which it was not prescribed. Do not share Lotronex

with other people. As with any medicine, LOTRONEX may be harmful without appropriate

medical supervision.

If you have questions about Lotronex, ask your doctor or pharmacist. They can show you

detailed information about Lotronex that was written for health professionals.

Inactive Ingredients: Lactose (anhydrous), magnesium stearate, microcrystalline cellulose,

and pregelatinized starch. The blue film-coat contains hydroxypropyl methylcellulose,

titanium dioxide, triacetin, and indigo carmine.

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

US Patent No. 5,360,800

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Date of Issue: February 2000 RL-XXX



EXHIBIT 5

United States Patent No. 5,360,800

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United States Patent [19]

Coates et al.

Patent Number: [11]

5,360,800

Date of Patent: [45]

Nov. 1, 1994

[54] TETRAHYDRO-1H-PYRIDO[4,3-B]INDOL-**1-ONE DERIVATIVES**

[75] Inventors: Ian H. Coates, Hertford; Peter C. North; Alexander W. Oxford, both of

Royston, all of England

[73] Assignee:

Glaxo Group Limited, London,

England

[*]. Notice:

The portion of the term of this patent subsequent to Feb. 2, 2010 has been

disclaimed.

[21] Appl. No.: 741,570

[22] Filed:

Aug. 7, 1991

Related U.S. Application Data

Continuation of Ser. No. 602,771, Oct. 24, 1990, abandoned, which is a continuation of Ser. No. 239,626, Sep. 2, 1988, abandoned.

[30] Foreign Application Priority Data

	ep. 3, 1987 [GB] g. 15, 1988 [GB]	United Kingdom 8720695 United Kingdom 8819382
[51]	Int. Cl.5	C07D 401/06; C07D 471/04;
		A61K 31/44; A61K 31/55
[52]	U.S. Cl	514/215; 514/292;
		540/524; 546/86; 546/87
[58]	Field of Search	546/85, 86, 87;
		540/524; 514/292, 215

[56] References Cited

U.S. PATENT DOCUMENTS

4,636,563	1/1987	Abou-Gharbia 546/87
4,695,578	9/1987	Coates et al 514/397

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

238411A1 9/1987 European Pat. Off. . 39-20857 9/1964 Japan 2180535B 4/1987 United Kingdom .

OTHER PUBLICATIONS

Fozard, TIPS, 8, Dec. 1987, pp. 501-506. King et al., Drugs of the Future, 14(9), 1989, pp. 875-889. Abou-Gharbia et al., J. Med. Chem., 1987, 30, 1818-1823.

Primary Examiner-Alan L. Rotman Attorney, Agent, or Firm-Bacon & Thomas

ABSTRACT

The invention relates to tricyclic lactams of the general formula (I)

wherein Im represents an imidazolyl group of the for-

and R1 represents a hydrogen atom or a group selected from C1-6alkyl, C3-6alkenyl, C3-10alkynyl, C3.7cycloalkyl, C3.7cycloalkylC1_4alkyl, phenyl, phenyl C1-3alkyl, phenylmethoxymethyl, phenoxyethyl or phenoxymethyl,

one of the groups represented by R2, R3 and R4 is a hydrogen atom or a C1-6alkyl, C3-7cycloalkyl, C3-6alkenyl, phenyl or phenyl C1-3alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C1-6alkhyl group;

n represents 2 or 3; and physiologically acceptable salts and solvates thereof.

The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT3 receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

35 Claims, No Drawings

Page 2

U.S. PAT			Abou-Gharbia et al 546/87	
		4,808,581	2/1989	Oxford et al 514/212
	Coates et al 514/397	4,814,344	3/1989	Humber et al 514/397
4,739,072 4/1988	Oxford et al 548/336	4.822.881	4/1989	Coates et al 540/603
4,749,718 6/1988	Coates et al 514/397			North et al 514/215
4,754,038 6/1988	Abou-Gharbia 546/87	5,183,820	2/1993	Coates et al 514/292

TETRAHYDRO-1H-PYRIDO[4,3-B]INDOL-1-ONE DERIVATIVES

This application is a continuation of application Ser. 5 No. 07/602,771, filed Oct. 24, 1990, abandoned which is a continuation of application Ser. No. 07/239,626, filed Sep. 2, 1988, now abandoned.

This invention relates to lactam derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

The present invention to the general formula (I):

In particular the invention relates to compounds which are potent and selective antagonists of 5-hydroxytryptamine (5-HT) at 5-HT receptors of the type located on terminals of primary afferent nerves. Receptors of this type are now designated as 5-HT receptors and are also present in the central nervous system. 5-HT occurs widely in the neuronal pathways in the central nervous system and disturbance of these 5-HT containing pathways is known to alter behavioural syndromes such as mood, psychomotor activity, appetite and memory.

Compounds having antagonist activity at 5-HT₃ receptors have been described previously.

Thus for example published UK Patent Specification No. 2153821A and published European Patent Specifications Nos. 191562, 219193 and 210840 disclose 3-imidazolylmethyltetrahydrocarbazolones which may be represented by the general formula:

wherein R¹ represents a hydrogen atom or a group selected from C₁₋₁₀alkyl, C₃₋₆ alkenyl, C₃₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, phenyl or phenylC₁₋₃alkyl, and in the case where Q represents a hydrogen atom, R¹ may also represent —CO₂R⁵, —COR⁵, —CONR⁵R⁶ or —SO₂R⁵ (wherein R⁵ and R⁶, which may be the same or different, each represents a hydrogen atom, a C₁₋₆ alkyl or C₃₋₇cycloalkyl group, or a phenyl or phenyl group is optionally substituted by one or more C₁₋₄ alkyl, C₁₋₄alkoxy or hydroxy groups or halogen atoms, with the proviso that R⁵ does not represent a hydrogen atom when R¹ represents a group —CO₂R⁵ 55 or —SO₂R⁵);

one of the groups represented by R², R³ and R⁴ is a hydrogen atom or a C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl, or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or 60 different, represents a hydrogen atom or a C₁₋₆ Suitable physiologically alkyl group;

Q represents a hydrogen atom or a halogen atom or a hydroxy, C₁₋₄alkoxy, phenylC₁₋₃alkoxy or C₁₋₆ alkyl group or a group —NR⁷R⁸ or —CONR⁷R⁸ 65 (wherein R⁷ and R⁸, which may be the same or different, each represents a hydrogen atom or a C₁₋₄ alkyl or C₃₋₄ alkenyl group, or together with

the nitrogen atom to which they are attached form a saturated 5 to 7 membered ring);

and physiologically acceptable salts and solvates

We have now found a noval group of compounds which differ in structure from those described previously, and which are potent antagonists of the effect of 5-HT at 5-HT₃ receptors.

The present invention provides a tricyclic lactam of the general formula (I):

wherein Im represents an imidazolyl groups of the

$$\mathbb{R}^4$$
 \mathbb{R}^4
 \mathbb{R}^4
 \mathbb{R}^4
 \mathbb{R}^4
 \mathbb{R}^4
 \mathbb{R}^4

and R¹ represents a hydrogen atom or a group selected from C₁₋₆alkyl, C₃₋₆alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄ alkyl, phenyl, phenylC₁₋₃alkyl, phenylmethoxymethyl, phenoxyethyl, phenoxymethyl, —CO₂R⁵, —COR⁵, —CONR⁵R⁶ or —SO₂R⁵ (wherein R⁵ and R⁶, which may be the same or different, each represents a hydrogen atom, a C₁₋₆ alkyl or C₃₋₇ cycloalkyl group, or a phenyl or phenylC₁₋₄alkyl group, in which the phenyl group is optionally substituted by one or more C₁₋₄ alkyl, C₁₋₄ alkoxy or hydroxy groups or halogen atoms, with the proviso that R⁵ does not represent a hydrogen atom when R¹ represents a group —CO₂R⁵ or —SO₂R⁵);

one of the groups represented by R², R³ and R⁴ is a hydrogen atom or a C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₆salkenyl, phenyl or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆ alkyl group;

n represents 2 or 3; and physiologically acceptable salts and solvates thereof.

According to one aspect, the invention provides compounds of formula (1) wherein R¹ represents a hydrogen atom or a group selected from C₁₋₆ alkyl, C₃₋₆ alkenyl, C₃₋₁₀ alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄ alkyl, phenyl or phenylC₁₋₃ alkyl (n and Im being as defined in formula (1)).

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonate), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates. The solvents may, for example, be hydrates. 3

All optical isomers of compounds of general formula (I) and their mixtures including the racemic mixtures thereof, and all the geometric isomers of compounds of formula (I), are embraced by the invention.

Referring to the general formula (I), an alkyl group 5 may be a straight chain or branched chain alkyl group, for example, methyl, ethyl, n-propyl, prop-2-yl, n-butyl, but-2-yl, 2-methylprop-2-yl, n-pentyl, pent-3-yl or nhexyl, A C₃₋₆ alkenyl group may be, for example, a propenyl or butenyl group. When R1 represents a C3. 10 6alkenyl or C₃₋₁₀alkynyl group, or R³ represents a C₃. 6alkenyl group, or R7 or R8 represents a C3-4alkenyl group, the double or triple bond may not be adjacent to the nitrogen atom. A phenylC₁₋₃alkyl group may be, for example, a benzyl, phenethyl or 3-phenylpropyl group. 15 A C3.7cycloalkyl group may be, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group.

A preferred class of compounds of formula (I) is that wherein R¹ represents a hydrogen atom or a C₁₋₆ alkyl 20 (e.g. methyl, ethyl, n-propyl, prop-2-yl), C₃₋₄ alkenyl (e.g. prop-2-enyl), C₃₋₄ alkynyl (e.g. prop-2-ynyl), C₅₋ scycloalkyl (e.g. cyclopentyl), C5-6cycloalkylmethyl (e.g. cyclopentylmethyl), phenylC₁₋₂ alkyl (e.g. benzyl), phenylmethoxymethyl, N,N-diC₁₋₃alkylcarboxamido 25 (e.g. N,N-dimethylcarboxamido) or C1-3alkylsulphonyl (e.g. methylsulphonyl) group. More preferably R¹ represents a C1-4 alkyl (e.g. methyl or n-propyl), C3-4alkynyl (e.g. prop-2-ynyl), C5-6cycloalkyl (e.g. cyclopentyl), C₅₋₆cycloalkylmethyl (e.g. cyclopentylmethyl), 30 nates (following the general procedure described by G. phenylC_{1.2} alkyl (e.g. benzyl), phenylmethoxymethyl, or N,N-diC₁₋₃alkylcarboxamido (e.g. N,N-dimethylcarboxamido) group.

Another preferred class of compounds of formula (I) is that wherein R² represents a hydrogen atom or a C₁₋₃ 35 antagonists of 5-HT at 5-HT₃ receptors, certain comalkyl (e.g. methyl) group, more preferably a hydrogen atom.

Another preferred class of compounds of formula (I) is that wherein R3 represents a hydrogen atom or a C1-3 alkyl (e.g. methyl) group, more preferably a hydrogen 40 rahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)meatom.

A further preferred class of compounds of formula (I) is that wherein R4 represents a hydrogen atom or a C1-3 alkyl (e.g. methyl or n-propyl) group. Most preferably r4 represents a methyl group.

When R² and R³ represent hydrogen atoms, R⁴ is preferably C1-6alkyl, C3-7 cycloalkyl, C3-6 alkenyl or phenylC₁₋₃alkyl, more particularly C₁₋₆ alkyl.

A further preferred class of compounds of formula (I) is that wherein n represents 2.

A preferred group of compounds of formula (I) is that wherein R1 represents a hydrogen atom or a C1-4 alkyl, C3-4alkenyl, C3-4alkynyl, C5-6cycloalkyl, C5-6cycloalkylmethyl, phenylC₁₋₂ alkyl, phenylmethoxymethyl, N,N-diC₁₋₃alkylcarboxamido or C₁₋₃alkylsul- 55 phonyl group; R2 represents a hydrogen atom; and R3 and r4 each represent a hydrogen atom or a C1-3 alkyl

A particularly preferred group of compounds of formula (I) is that wherein R1 represents a methyl, n-pro- 60 pyl, prop-2-ynyl, cyclopentyl, cyclopentylmethyl, benzyl or N,N-dimethylcarboxamido group; R2 and R3 each represent a hydrogen atom; and R4 represents a methyl group.

Within the above preferred and particularly pre- 65 ferred groups of compounds, an especially important group of compounds is that in which n represents 2.

Preferred compounds according to the invention are:

- 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1Himidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one;
- 2,3,4,5-tetrahydro-5-(phenylmethyl)-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-
- 5-cyclopentyl-2,3,4,5-tetrahydro-2-[(5-methyl-1Himidazol-4yl)-methyl]-1H-pyrido[4,3-b]indol-
- 2,3,4,5-tetrahydro-2[(5-methyl-1H-imidazol-4-yl)methyl]-5-propyl-1H-pyrido[4,3-b]indol-1-one;
- 5-(cyclopentylmethyl)-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl) methyl]-1H-pyrido[4,3-b]indol-1-one:
- 3,4,5,6-tetrahydro-6-methyl-2-[(5-methyl-1Himidazol-4-yl)methyl]-azepino[4,3-b]indol-1(2H)-onc
- 2,3,4,5-tetrahydro-N,N-dimethyl-2-[(5-methyl-1Himidazol-4yl)-methyl]-1-oxo-5H-pyrido[4,3-b]indole-5-carboxamide;
- 2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propynyl)-1H-pyrido[4,3-b]indol-1-one; and their physiologically acceptable salts and solvates.

The potent and selective antagonism of 5HT at 5-HT₃ receptors by compounds of the invention has been demonstrated by their ability to inhibit 3-(5-methyl-1H-imidazol-4yl)-1-[1-(methyl-t₃)-1H-indol-3yl]-1propanone binding in rat entorhinal cortex homoge-Kilpatrick et al. in Nature, 1987, 330, 746), and/or by their ability to inhibit the 5-HT-induced depolarisation of the rate isolated vagus nerve preparation.

In addition to their activity as potent and selective pounds according to the invention have the advantage of an extended duration of action.

a particularly preferred compound on account of both its potency and duration of action is 2,3,4,5-tetthyl]-1H-pyrido[4,3-b]indol-1-one and its physiologically acceptable salts and solvates. Preferred salts of this compound are the hydrochloride and maleate.

Compounds of formula (I), which antagonise the effect of 5-HT at 5-HT₃ receptors, are useful in the treatment of conditions such as psychotic disorders (e.g. schizophrenia and mania); anxiety; and nausea and vomiting, particularly that associated with cancer chemotherapy and radiotherapy. Compounds of formula (I) 50 are also useful in the treatment of gastric stasis; symptoms of gastrointestinal dysfunction such as occur with dyspepsia, peptic ulcer, reflux oesophagitis, flatulence and irritable bowel syndrome; migraine; and pain. Compounds of formula (I) may also be used in the treatment of dependency on drugs and substances of abuse, depression, and dementia and other cognitive disorders.

According to another aspect, the invention provides a method of treatment of a human or animal subject suffering from a psychotic disorder such as schizophrenia or mania; or from anxiety; nausea or vomiting; gastric stasis; symptoms of gastrointestinal dysfunction such as dyspepsia, reflux oesophagitis, peptic ulcer, flatulence and irritable bowel syndrome; migraine; or pain, which comprises administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound selected from compounds of the general formula (I), and their physiologically acceptable salts and solvates (e.g. hydrates), for use in human or veterinary medicine, and formulated for administration by any convenient route.

Such compositions may be formulated in conventional manner using one or more physiologically acceptable carriers and/or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or cap- 15 sules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxylpropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phos- 20 phate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparation for oral adminis- 25 tration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically 30 acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preserva- 35 tives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably 40 formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The 50 compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with 55 a suitable vehicle, e.g. sterily pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or

hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

For intra nasal administration, the compounds according to the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

The compounds of formula (I) may also be administered in combination with other therapeutic agents. Thus, for example, in the treatment of gastric stasis, symptoms of gastrointestinal dysfunction and nausea and vomiting, the compounds of formula (I) may be administered in combination with antisecretory agents such as histamine H₂-receptor antagonists (e.g. ranitidine, sufotidine, 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol, cimetidine, famotidine, nizatidine or roxatidine) or H+K+ATPase inhibitors (e.g. omeprazole).

A proposed dose of the compounds of the invention for administration to man (of approximately 70 kg body weight) is 0.001 to 100 mg, preferably 0.01 to 50 mg, more preferably 0.1 to 20 mg of the active ingredient per unit dose expressed as the weight of free base, which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient. The dosage will also depend on the route of administration.

Compounds of general formula (I) and physiologically acceptable salts or solvates thereof may be prepared by the general methods outlined hereinafter. In the following description, the groups R¹, n, and Im are as defined for compounds of general formula (I) unless otherwise stated.

According to a first general process (A), a compound of general formula (I) may be prepared by alkylating a compound of formula (II):

with a compound of formula (III):

or a protected derivative thereof, wherein L represents a leaving atom or group, such as a halogen atom (e.g. chlorine, bromine or iodine), or an acyloxy group (e.g. trifluoroacetyloxy or acetoxy), or a sulphonyloxy group (e.g. trifluoromethanesulphonyloxy, ptoluenesulphonyloxy or methanesulphonyloxy), followed wherein necessary by removal of any protecting groups. L is preferably a halogen atom (e.g. a chlorine atom).

The reaction may be carried out in an inert solvent 10 such as an ether (e.g. dimethoxyethane, diglyme or tetrahydrofuran), a substituted amide (e.g. dimethylformamide or N-methylpyrrolidone), an aromatic hydrocarbon (e.g. toluene), a ketone (e.g. acetone), or dimethyl sulphoxide, at a temperature between ambient and 100° C., in the presence of a base. Suitable bases include alkali metal hydrides (e.g. sodium hydride), alkali metal carbonates (e.g. sodium carbonate), alkali metal amides (e.g. sodium amide), alkali metal alkoxides (e.g. potassium t-butoxide) or alkali metal hydroxides (e.g. sodium or potassium hydroxide).

According to another general process (B), a compound of general formula (I) wherein n represents 2, may be prepared by hydrogenation of a compound of formula (IV):

or a protected derivative thereof, followed where necessary by removal of any protecting groups.

Hydrogenation according to general process (B) may be effected using conventional procedures, for example using hydrogen in the presence of a noble metal catalyst (e.g. palladium, Raney nickel, platinum or rhodium). The catalyst may be supported on, for example, charcoal or alumina, or alternatively a homogeneous catalyst such as tris(triphenylphosphine)rhodium chloride may be used. The hydrogenation will generally be effected in a solvent such as an alcohol (e.g. methanol or ethanol), an ether (e.g. dioxan), or an ester (e.g. ethyl accetate), or in a mixture of an alcohol and either a hydrocarbon (e.g. dichloromethan), at a temperature in the range 50 carbon tetrachloride) and 50 carbon tetrachloride)

According to another general process (C), a compound of general formula (I) may be prepared by cyclising a compound of formula (V):

wherein W represents a hydrogen atom and Y represents the group NH, or W represent a halogen atom and Y represents a bond, or a salt or protected

derivative thereof, followed where necessary by removal of any protecting groups.

According to one embodiment (a) of process (C), the reaction is effected with a compound of formula (V) wherein W represents a hydrogen atom and Y represents the group NH, and the cyclisation may be carried out in aqueous or non-aqueous media, in the presence of an acid catalyst.

It will be appreciated that these compounds of formula (V) may exist in the corresponding enol hydrazone tautomeric form.

When an aqueous medium is employed this may be water or a mixture of water and a organic solvent such as an alcohol (e.g. methanol, ethanol or isopropanol) or an ether (e.g. dioxan or tetrahydrofuran). The acid catalyst may be, for example, an inorganic acid such as concentrated hydrochloric or sulphuric acid. In some cases the acid catalyst may also act as the reaction solvent. In an anhydrous reaction medium, which may comprise one or more alcohols or ethers (e.g. as described above), carboxylic acids (e.g. acetic acid) or esters (e.g. ethyl acetate), the acid catalyst may alternatively by a Lewis acid such as boron trifluoride, zinc chloride or magnesium chloride. The cyclisation reaction may conveniently be carried out at temperatures of from 20° to 200° C., preferably 20° to 125° C.

Alternatively the cyclisation according to embodiment (a) of process (C) may be carried out in the pressure of polyphosphate ester in a reaction medium which may comprise one or more organic solvents, preferably halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, dichlorodifluoromethane, or mixtures thereof. Polyphosphate ester is a mixture of esters which may be prepared from phosphorus pentoxide, diethyl ether and chloroform according to the method described in 'Reagents for Organic Synthesis', (Fieser and Fieser, John Wiley and Sons, 1967).

According to another embodiment (b) of process (C), the reaction is effected with a compound of formula (V) wherein W represents a halogen atom, for example, a chlorine atom or, more preferably, a bromine or iodine atom, Y represents a bond, and the cyclisation is effected photochemically.

The reaction may conveniently be effected by irradiating with a mercury lamp, preferably a medium or high pressure mercury lamp. Suitable solvents include nitriles (e.g. acetonitrile), chlorinated hydrocarbons (e.g. carbon tetrachloride) and cyclic ethers (e.g. tetrahydrofuran or dioxan) and mixtures thereof. The reaction may conveniently be effected in the presence of abase such as a tertiary amine (e.g. triethylamine).

According to another general process (D), a compound of general formula (I) wherein R³ represents a hydrogen atom, may be prepared by the reaction of a compound of formula (VI):

or a protected derivative thereof, with formamide, at a temperature in the range of 150° to 200° C., followed where necessary by removal of any protecting groups.

According to another general process (E), a compound of general formula (I) may be prepared by react- 5 ing a compound of formula (VII):

$$(VII)$$

$$(CH_2)_nNHCH_2Im$$

wherein G represents a hydrogen atom, or a protected derivative thereof, with phosgene in the presence of a Lewis acid; or by reacting a compound of formula (VII) wherein G represents an iodine or a bromine 20 atom, or a protected derivative thereof, with carbon monoxide in the presence of a palladium (II) salt, followed where necessary by removal of any protecting groups.

According to one embodiment of process (E), a compound of formula (VII), wherein G represents a hydrogen atom, is reacted with phosgene in the presence of a Lewis acid such as anhydrous aluminium trichloride or stannic chloride. The reaction may conveniently by effected in an inert solvent such as an aromatic hydrocarbon (e.g. toluene) or a halogenated hydrocarbon 30 (e.g. dichloromethane), or mixtures thereof, and at a temperature between ambient and 100° C.

According to another embodiment of process (E), a compound of formula (VII), wherein G represents an iodine or a bromine atoms, is reacted with carbon mon- 35 oxide in the presence of a palladium (II) salt (e.g. palladium acetate or palladium chloride) and preferably in the presence of triphenylphosphine. The reaction may conveniently be effected in a solvent such as a tertiary amine (e.g. tri-n-butylamine), optionally in the presence 40 of a co-solvent such as an ether (e.g. tetrahydrofuran) or an aromatic hydrocarbon (e.g. toluene), at a temperature in the range 100° to 150° C., and at atmospheric

According to another general process (F), a com- 45 pound of general formula (I) may be converted into another compound of formula (I) using conventional techniques. Such conventional techniques include hydrogenation, alkylation and acylation using protection and deprotection where necessary.

Thus, according to one embodiment of the interconversion process (F), hydrogenation may be used to convert an alkenyl or an alkynyl substituent into an alkyl substituent, or an alkynyl into an alkenyl substituent. Hydrogenation may also be used to replace a phe- 55 Beckmann rearrangement of an oxime of formula nylmethoxymethyl group by a hydrogen atom. Hydrogenation according to general process (F) may be effected using conventional procedures, for example, using hydrogen in the presence of a catalyst, as described above in general process (B).

The term 'alkylation' according to general process (F) includes the introduction of groups such as cycloalkvi, alkenyl or phenalkyl groups.

Thus, for example, a compound of formula (I) in which R1 represents a C1-6 alkyl, C3-6 alkenyl, C3-10 65 alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₄ alkyl, phenyl C1.3 alkyl, phenylmethoxymethyl, phenoxyethyl or phenoxymethyl group may be prepared by alkylating

a compound of formula (I) in which R1 represents a hydrogen atom, or a compound in which R3 represents a C1-6alkyl, C3-7cycloalkyl, C3-6alkenyl or phenylC1-3alkyl group may be prepared by alkylating the corresponding compound of formula (I) in which R3 represents a hydrogen atom, using conventional procedures, for example as described in published may be effected using an appropriate alkylating agent of formula R⁷Z (where R⁷ is the group to be introduced and Z is a leaving atom or group), preferably in the presence of a

According to another embodiment of general process (F), a compound of formula (I) wherein R1 represents -CO₂R⁵, -COR⁵, -CONR⁵R⁶ or -SO₂R⁵ may be prepared by acylating or sulphonylating as appropriate, a compound of formula (I) wherein R1 represents a hydrogen atom. The acylation/sulphonylation reactions may be effected using an appropriate acylating-/sulphonylating agent according to conventional procedures, for example, as described in published European Patent Specification No. 210840.

It should be appreciated that in the above transformations it may be necessary or desirable to protect any sensitive groups in the molecule of the compound in question to avoid undesirable side reactions. For example, it may be necessary to protect the indole and/or imidazole nitrogen atoms, for example with an arylmethyl (e.g. trityl), arylmethoxymethyl (e.g. phenylmethoxymethyl), alkyl (e.g. t-butyl), alkoxymethyl (e.g. methoxymethyl), acyl (e.g. benzyloxycarbonyl) or a sulphonyl (e.g. N,N-dimethylaminosulphonyl or ptoluenesulphonyl) group.

Thus according to another general process (G), a compound of general formula (I) may be prepared by the removal of any protecting groups from a protected form of a compound of formula (I). Deprotection may be effected using conventional techniques such as those described in 'Protective Groups in Organic Synthesis' by T. S. Greene (John Wiley and sons, 1981).

For example, an arylmethoxymethyl N-protecting group may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal). A trityl group may be cleaved by acid hydrolysis (e.g. using dilute hydrochloric or acetic acid). An alkoxyalkyl group may be removed using a mineral acid (e.g. dilute hydrochloric or hydrobromic acid). An acyl group may be removed by hydrolysis under acidic or basic conditions (e.g. using hydrogen bromide, dilute hydrochloric acid or sodium hydroxide). A sulphonyl group may also be removed by alkaline or acidic hydrolysis, and an N, N-dimethylaminosulphonyl group may also be removed (e.g. from an imidazole nitrogen atom) by photolysis.

Compounds of formula (II) may be obtained by a (VIII):

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wherein m represents 1 or 2, or a protected derivative thereof. The Beckmann rearrangement may be effected using conventional methods, for example by using an acid (e.g. polyphosphoric or sulphuric acid, or a mixture of hydrochloric acid, acetic anhydride and acetic acid) in an inert solvent such as an ether (e.g. dioxan), an amide (e.g. dimethylformamide) or a hydrocarbon (e.g. toluene or cyclohexane), at an elevated temperature of, for example, 50° to 120° C. Alternatively, the hydroxy 10 group of the oxime of formula (VIII), may be converted into a leaving group such as a chloride (using, for example, phosphorus pentachloride) or a hydrocarbylsulphonate (e.g. a mesylate or a tosylate) or a trifluoroacetate group (using conventional acylation methods). Subsequent heating at a temperature of, for example, 20° to 150° C., in an inert solvent as described above, gives a compound of formula (II).

Compounds of formula (VIII) may be prepared from 20 the corresponding tricyclic ketone of formula (IX):

$$(CH_2)_m$$

wherein m represents 1 or 2, or a protected derivative thereof using conventional methods, for example by using hydroxylamine hydrochloride in a solvent 35 such as pyridine.

Compounds of formula (IV) may be prepared, for example, by reacting a compound of formula (X):

or a protected derivative thereof, with a compound of formula (III) wherein L is as defined previously, or a protected derivative thereof, using the conditions described in process (A).

Compounds of formula (X) may be prepared by heating a compound of formula (II) wherein n represents 2, with a noble metal catalyst such as palladium, palladium oxide, platinum or nickel, at a temperature of, for example, 300° to 350° C. The catalyst may be supported on, for example, charcoal or alumina, and the reaction may optionally be carried out in the presence of an inert solvent such as an aromatic hydrocarbon (e.g. p-cymene)

Compounds of formula (V) wherein W represents a 65 hydrogen atom and Y represents the group NH may be prepared by the reaction of a compound of formula. (XI):

or a salt thereof, with a compound of formula (XII):

or a protected derivative thereof, in a suitable solvent such as an aqueous alcohol (e.g. methanol), and at a temperature of, for example, from 20° to 100° C.

A protected derivative of a compound of formula (XII) may for example have the keto carbonyl group protected (e.g. as an enol ether). It will be appreciated that when a compound of formula (XII) is used in which the keto carbonyl group is protected, it may be necessary to remove the protecting group in order for reaction to occur with the compound of formula (XI). Deprotection may be carried out by conventional methods, for example by acidic hydrolysis (e.g. using dilute sulphuric or hydrochloric acid). If desired, deprotection may be effected in situ.

Compounds of formula (XII) may be prepared, for example, by reacting a compound of formula (XIII):

or a protected derivative thereof, with a compound of formula (III) wherein L is as defined previously, or a protected derivative thereof, using the conditions described in process (A).

Compounds of formula (V) wherein W represents a halogen atom and Y represents a bond may be prepared, for example, by reacting a compound of formula (XIV):

$$(XIV)$$

$$W$$

$$NH$$

$$|$$

$$|$$

$$(CH_2)_n$$

wherein W represents a halogen atom, or a protected derivative thereof, with a compound of formula (III) wherein L is as defined previously, or a protected derivative thereof, using the conditions described in process (A).

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Compounds of formula (XIV) may be prepared by reacting a compound of formula (XV):

with a compound of formula (XIII), at an elevated temperature.

Compounds of formula (VI) may be prepared, for example, by reacting a compound of formula (II), or a protected derivative thereof, with a compound of formula (XVI):

wherein L is as defined previously, using the condi- 25 in the final product. tions described in process (A).

The invention is f

Compounds of formula (VII) wherein G represents a halogen atom may be prepared, for example by reacting a compound of formula (VII) wherein G represents a hydrogen atom, or a protected derivative thereof, with 30 an appropriate halogen and alkali metal halide (e.g. iodine and potassium iodide), in a suitable solvent such as an aqueous alcohol (e.g. aqueous ethanol).

Compounds of formula (VII) wherein G represents a hydrogen atom may be prepared, for example, by reacting a compound of formula (XVII):

ing a compound of formula (XVII):

indicated, over magnesium sulphate or sodium sulphate.

The following abbreviations are used: DMF - dimethyling a compound of formula (XVII):

$$(XVII)$$

$$\downarrow \\ \downarrow \\ \downarrow \\ R^1$$

$$(CH_2)_nNH_2$$

or a protected derivative thereof, with a compound of formula (III) wherein L is as defined previously, or a protected derivate thereof, using the conditions described in process (A).

Compounds of formula (III) and protected derivative 50 thereof, are either known, or may be prepared, for example, by the methods described in German Offenlegungsschrift No. 3740352.

Compounds of formula (IX) may be prepared, for example, by the method or methods analogous to that 55 described by H. Iida et al. in *J. Org. Chem.*, 1980, 45, 2938.

Compounds of formulae (XI), (XIII), (XV), (XVI) and (XVII) are either known, or may be prepared from known compounds by conventional procedures.

Where it is desired to isolate a compound of the invention as a salt, for example a physiologically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate acid, preferably with an equivalent amount, 65 in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an aqueous alcohol (e.g. aqueous ethanol), a halogenated hydrocarbon (e.g. dichloromethane), an

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ester (e.g. ethyl acetate) or an ether (e.g. tetrahydrofuran).

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of formula (I) using conventional methods.

Individual enantiomers of the compounds of the invention may be obtained by resolution of a mixture of 10 enantiomers (e.g. a racemic mixture) using conventional means, such as an optically active resolving acid; see for example 'Stereochemistry of Carbon Compounds' by E. L. Eliel (McGraw Hill, 1962) and 'Tables of Resolving Agents' by S. H. Wilen.

The methods described above for preparing the compounds of the invention may be used for the introduction of the desired groups at any stage in the stepwise formation of the required compounds, and it will be appreciated that these methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

The invention is further illustrated by the following Intermediates and Examples. All temperatures are in °C. Thin layer chromatography (t.l.c.) was carried out on silica, and flash column chromatography (FCC) on silica (Merck 9385), solvent System A as used for chromatography denotes dichloromethane:ethanol:0.88 ammonia solution. Organic extracts were dried, where indicated, over magnesium sulphate or sodium sulphate. The following abbreviations are used: DMF - dimethylforamide; THG - tetrahydrofuran; DME - dimethoxyethane. ¹H-N,m.r. spectra were obtained at 250 MHz for dilute solutions in d₆-dimethyl sulphoxide.

Intermediate 1

4-(Chloromethyl)-1-(triphenylmethyl)-1H-imidazole

Thionyl chloride (0.82 g) was added over 1 min. to a stirred suspension of 1-(triphenylmethyl)-1H-imidazole-45 4-methanol (1.3 g) in a mixture of dichloromethane (50 ml) and DMF (1.0 ml) at 23°. The solution so obtained was stirred for 15 min. and extracted with 8% sodium bicarbonate solution (80 ml). The organic phase was washed with water (50 ml), dried and evaporated to give an oil which solidified. The solid was slurried in hexane and filtered to give the title compound (1.28 g), m.p. 139'-141°.

Intermediate 2

4-Formyl-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide

Demethylsulphamoyl chloride (0.67 ml) was added to a stirred solution of 5-propyl-1H-imidazole-4-carbox-aldehyde (860 mg) and triethylamine (0.87 ml) in dry dichloromethane (10 ml) under nitrogen. The solution was heated at reflux for 24 h, allowed to cool, poured into water (50 ml) and extracted with dichloromethane (3×25 ml). The combined, dried organic extracts were evaporated to give an oil (1.9 g) which was purified by FCC eluting with ethyl acetate:hexane (1:1) to give the title compound (500 mg), m.p. 57°-58°.

Intermediate 3

4-(Hydroxymethyl)-N,N-dimethyl-5-propyl-1Himidazole-1-sulphonamide

Sodium borohydride (139 mg) was added to a stirred solution of 4-formyl-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide (450 mg) in absolute ethanol (5 ml) under nitrogen. After 3 h the mixture was poured into water (30 ml) and extracted with dichloromethane $(3 \times 15 \text{ ml})$. The combined, dried organic extracts were evaporated to give a solid (425 mg) which was triturated with ether $(2 \times 10 \text{ ml})$ to give the title compound (350 mg), m.p. 86° - 88° .

Intermediate 4

4-(Chloromethyl)-N,N-dimethyl-5-propyl-1Himidazole-1-sulphonamide

A solution of thionyl chloride (0.12 ml) in dry dichloromethane (1.2 ml) was added dropwise to a cold (0°) stirred solution of 4-(hydroxymethyl)-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide (340 mg) in dry dichloromethane (7.5 ml) under nitrogen. After 1.5 h the solution was washed with 8% sodium bicarbonate solution (2×15 ml) and the aqueous phase was extracted with dichloromethane (2×10 ml). The combined organic extracts were washed with water (15 ml), dried and evaporated to give the title compound (180 ml) as an oil, t.l.c. (ethyl acetate) Rf 0.68.

Intermediate 5

3,4-Dihydro-4-methylcyclopent[b]indol-1(2H)-one oxime

3,4-Dihydro-4-methylcyclopent[b]indol-1(2H)-one (1.7 g) and hydroxylamine hydrochloride (1.925 g) in pyridine were heated at 60° for 18 h and cooled. The reaction mixture was evaporated in vacuo to a residue to which was added 8% sodium bicarbonate (150 ml). Extraction with ethyl acetate (300 ml) produced a suspension in the organic layer; this layer and associated solid was separated from the aqueous layer. The aqueous layer was re-extracted with ethyl acetate (250 ml). The combined organic extracts (and suspended solid) 45 were evaporated to a residue, boiled with a mixture of ethanol (150 ml) and methanol (150 ml) and cooled to ca. 50°. The residue was adsorbed from this solution on to FCC silica and applied to an FCC column. Elution with ethyl acetate/3-10% methanol provided the title 50 compound (1.69 g), m.p. 219°-224° (decomp.).

Intermediate 6

2,3,4,5-Tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one

3,4-Dihydro-4-methylcyclopent[b]indol-1(2H)-one oxime (1.53 g), polyphosphric acid (450 g) and dioxan (15 ml) were heated at 100°-120° for 2.2 h under nitrogen. The reaction mixture was cooled, and treated with 60 2N sodium carbonate solution (1 l). The suspension was extracted with ethyl acetate (4×400 ml) and the combined extracts were dried. Evaporation gave a solid (1.43 g) which was recrystallised from ethyl acetate/cyclohexane. This solid was purified by FCC, cluting with 65 System A (200:10:1) to give a solid (1.26 g) which was recrystallised from ethanol to provide the title compound (960 mg), m.p. 234°-238°.

Intermediate 7

3,4,5,6,-Tetrahydro-6-methylazepino[4,3-b]indol-1(2H)-one

1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one oxime (24 g) and polyphosphoric acid (600 g) in dioxan (500 ml) were treated according to the method described for Intermediate 6. The solid (22 g) obtained by evaporation of the organic extracts was recrystallised from ethyl acetate (300 ml) to give a solid (19.2 g). This was purified by FCC eluting with System A (200:8:1) to give the title compound (5.5 g), m.p. 212°-215°.

Intermediate 8

5,6-Dihydro-4-(phenylamino)-1(2H)-pyridinone

A mixture of 2,4-dioxopiperidine (1.13 g) and aniline (930 mg) was heated at 120° under a stream of nitrogen for 15 min. The resultant solid was triturated with ether and filtered off to give the title compound (1.74 g), m.p. 235°-238°.

Intermediate 9

2,3,4,5-Tctrahydro-1H-pyrido[4,3-b]indol-1-one

A solution of 5,6-dihydro-4-(phenylamino)-1(2H)pyridinone (1.5 g) and palladium acetate (150 mg) in dry
DMF (50 ml) was treated with cupric acetate (3.2 g)
and the resulting mixture was heated under nitrogen at
120°-130° for 1.5 h. The mixture was then concentrated
in vacuo to give a solid which was triturated with 2N
hydrochloric acid (250 ml). The acid was decanted, and
the remaining solid was extracted with ethyl acetate for
18 h. The decanted acid was basified with 2N sodium
hydroxide and extracted with ethyl acetate (3×100 ml).

These organic extracts were combined with the previous ethyl acetate extracts and adsorbed onto silica. Purification by FCC eluting with System A (100:8:1) gave
the title compound (874 mg), m.p. 212°-215°.

Intermediate 10

2,3,4,5-Tetrahydro-5-[(phenylmethoxy)methyl]-1Hpyrido[4,3-b]indol-1-one

a solution of 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one (1.12 g) in dry DMF (60 ml) was treated with sodium hydride (60% dispersion in oil; 480 mg) and the resulting mixture was stirred under nitrogen until effervescence ceased. The mixture was then cooled to 0° and benzyl (chloromethyl) ether (10% w/v solution in DMF; 0,835 ml) was added over 10 min. Stirring was continued for a further 5 min and then water (10 ml) was added. The reaction mixture was concentrated in vacuo to give an oil which was dissolved in ethyl acetate (100 ml) and washed with water (3×100 ml). The organic phase was dried and adsorbed onto FCC silica. Purification by FCC eluting with System A (150:8:1) gave the title compound 1.1 g), m.p. 133°-135°.

Intermediates 11 to 14 were prepared in a similar manner to Intermediate 10, i.e. by treating 2,3,4,5-tet-rahydro-1H-pyrido[4,3-b]indol-1-one with sodium hydride followed by an appropriate alkylating agent. Isolation and purification of the products were as described for Intermediate 10 unless otherwise stated.

Intermediate 11

5-Ethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one (931 mg) was treated with sodium hydride (60% dispersion

in oil; 400 mg) and was then stirred with ethyl iodide (10% v/v solution in DMF; 4 ml) to give the title compound (758 mg), m.p. 203*-204.5*.

Intermediate 12

2,3,4,5-Tetrahydro-5-(1-methylethyl)-1H-pyrido[4,3-b]indol-1-one

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one (931 mg) was treated with sodium hydride (73% dispersion in oil; 328 mg) and was then stirred with 2-bromopropane (615 mg) at room temperature for 72 h. Purification by FCC eluting with System A (200:8:1) gave a foam (324 mg) which was further purified by recrystallisation from ethyl acetate: hexane (1:1) to give the title compound (249 mg), t.l.c. (System A, 100:8:1) Rf 0.58.

Intermediate 13

2,3,4,5-Tetrahydro-5-(phenylmethyl)-1H-pyrido[4,3-b]indol-1-one

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one (559 mg) was treated with sodium hydride (73% dispersion in oil; 197 mg) and was then stirred with benzyl bromide (513 mg) at room temperature for 30 min. Purification by FCC eluting with dichloromethan: ethanol (80:1) 25 gave the title compound (347 mg), m.p. 209°-212°.

Intermediate 14

5-(Cyclopentylmethyl)-2,3,4,5-tetrahydro-1Hpyrido[4,3-b]indol-1-one

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one (950 mg) was treated with sodium hydride (60% dispersion in oil; 408 mg) and was then stirred with cyclopentahemethanol (methane sulphonate) (909 mg) at room temperature for 7 days. The solid (570 mg) obtained by FCC was further purified by slow evaporation form a solution in methanol to give the title compound, m.p. 179°-181°.

Intermediate 15

2,3,4,5-Tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of triphenylmethyl chloride (3.36 g) in dry DMF (40 ml) was added dropwise to a stirred solution of 2,3,4,5-tetrahydro-2-](5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (2.8 g) in dry DMF (50 ml) containing triethylamine (1.52 g). When addition was complete the mixture was stirred overnight. The mixture was then poured into water (1000 ml) and the resulting suspension was extracted with ethyl acetate (3×300 ml). The combined organic extracts were washed with water (2×500 ml), dried and concentrated onto silica. FCC cluting with System A (100:8:1) gave the title compound (4.3 g), m.p. 55 235°-236°.

Intermediate 16

2,3,4,5-Tetrahydro-5-methyl-2-[[1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one

A mixture of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (0.3 g) and sodium hydride (80% dispersion in oil; 0.05 g) in dry DMF (5 ml) was stirred under nitrogen at 50° until hydrogen evolution ceased (ca. 0.5 h). The mixture was cooled to 40° and a 65 solution of 4-(chloromethyl)-1-(triphenylmethyl)-1H-imidazole (0.53 g) in dry THF (3 ml) was added. The mixture was stirred at 40° to 23° over 2 h, poured into

water (100 ml) and extracted with dichloromethane (3×100 ml). The dried organic phase was evaporated to give a semi-solid which was purified by FCC eluting with dichloromethane:ethyl acetate:triethylamine (50:50:1) to give a solid. This was slurried in hexane and filtered to give the title compound (0.37 g), m.p. 205°-210° (decomp.).

Intermediate 17

2,5-Dihydro-5-methyl-1H-pyrido[4,3, -b]indol-1-one

A mixture of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (500 mg) and 10% palladium oxide on carbon catalyst (50% aqueous paste; 250 mg) was heated at 320° for 10 min. The cooled solid was triturated with ethanol (ca. 100 ml), filtered and the resulting filtrate was evaporated to give the title compound (470 mg), m.p. 242.5°.

Intermediate 18

2,5-Dihydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

Sodium hydride (73% dispersion in oil; 80 mg) was added to a stirred suspension of 2,5-dihydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (440 mg) in dry dimethoxyethane (25 ml) under nitrogen and the mixture was heated at 50° for 6 h. 4-(Chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (910 mg) was then added, and stirring was continued at 50° for 20 h. Water (4.5 ml) and acetic acid (4.5 ml) were added and the solution was heated at reflux for 5 h. The mixture was poured into 8% sodium bicarbonate solution (80 ml) and extracted with dichloromethan:ethanol (10:1; 3×40 ml). The combined, dried organic extracts were evaporated to give a solid (ca. 1.5 g) which was purified by FCC eluting with System A (100:10:1) to give the free base of the title compound as a solid (348 mg). A sample of this 40 solid (100 mg) was dissolved in absolute ethanol (20 ml) and treated with a solution of maleic acid (40 mg) in absolute ethanol (1 ml). The solvent was removed in vacuo and the residue was triturated with dry ether (3×20 ml) to give a solid (115 mg) which as re-crystallised from methanol-ethyl acetate to give the title compound (40 mg), m.p., 166°-168°.

Intermediate 19

5,6-Dihydro-4-methoxy-1-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-2(1H)-pyridinone

Sodium hydride (80% dispersion in oil; 360 mg) was suspended in dry DME (50 ml) under nitrogen and 5,6-dihydro-4-methoxy-2(1H)-pyridinone (1.27 g) in dry DME (20 ml) was added slowly. The resulting suspension was stirred at 20° for 1 h. 4-(Chloromethyl)-5methyl-1-(triphenylmethyl)-1H-imidazolc (3.72 g) in dry DME (50 ml) was added, and after the initial reaction had subsided the mixture was heated to 50° for 4 h and then cooled. Methanol (5 ml) was added dropwise, and solvent was removed invacuo. 8% Aqueous sodium bicarbonate solution (300 ml) was added to the residue and the resulting solution was extracted with dichloromethane (2×300 ml), dried and evaporated in vacuo to leave an oil which was purified by FCC eluting with System A (200:8:1) to give the title compound (2.84 g), m.p. 181°-184°.

Intermediate 20

2,4-Dioxo-1-[(5-methyl-1H-imidazol-4-yl)methyl]piperidine

To a solution of 5,6-dihydro-4-methoxy-1-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4yl]methyl]-2(1H)-pyridinone (500 mg) in THF (4 ml) was added hydrochloric acid (5M; 1 ml), and the mixture was stirred at 50° for 1 h. The solvent was removed in vacuo, triethylamine (1 ml) was added, and the mixture was again evaporated to dryness. FCC of the residue eluting with ethyl acetate:methanol:triethylamine (8:4:1) gave the title compound (139 mg), m.p. 100°-106° (decomp.).

Intermediate 21

5,6-Dihydro-1-](5-methyl-1H-imidazol-4-yl)methyl]-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone

2,4-Dioxo-1-[(5-methyl-1H-imidazol-4-yl)methyl]piperidine (200 mg) was dissolved in ethanol (2 ml) and 20
N-methylphenylhydrazine (26 mg) was added. The
mixture was stirred for 1 h and the solvent was removed
in vacuo. The residue was purified by FCC eluting with
system A (75:8:1) to give the title compound (24 mg) as
a solid, t.l.c. (System A, 75:8:1) Rf 0.27.

Intermediate 22

N,N,5-Trimethyl-4-[[(trimethylsilyl)oxy]methyl]-1Himidazole-1-sulphonamide

A suspension of 4-(hydroxymethyl)-5-30 methylimidazole hydrochloride (14.9 g) in dry dichloromethane (500 ml) containing triethylamine (50 g) was treated with trimethylsilyl chloride (21.7 g) and the reaction mixture was stirred at room temperature overnight. Dimethylsulphamoyl chloride (14.3 g) was added and the reaction mixture was again stirred at room temperature overnight. The resulting suspension was filtered and the collected solid was washed with dichloromethane (100 ml). The filtrate was concentrated onto silica and purification by FCC eluting with hexane:e-ther (4:1) gave the title compound as an oil (7.2 g), t.l.c. (cther) Rf 0.5.

Intermediate 23

4-(Hydroxymethyl)-N,N5-trimethyl-1H-imidazole-1- 45 sulphonamide

A solution of N,N,5-trimethyl-4-[[(trimethylsilyl)ox-y]methyl]-1H-imidazole-1-sulphonamide (2.59 g) in dry THF (50 ml) was treated with a solution of tetrabutylammonium fluoride (1M solution in THF; 10 ml), and the THF was immediately removed in vacuo. The residue was partitioned between water (100 ml) and dichloromethane (100 ml) and the aqueous layer was extracted with dichloromethane (100 ml). The combined, dried organic fractions were concentrated to give the title compound (1.63 g) as a solid, m.p. 134°-136°.

Intermediate 24

4-(Chloromethyl)-N,N,5-trimethyl-1H-imidazole-1-sulphonamide

A suspension of 4-(hydroxymethyl)-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (2.86 g) in dry dichloromethane (200 ml) containing DMF (0.5 ml) was treated 65 dropwise with a solution of thionyl chloride (1.178 g) in dichloromethane (10 ml). The reaction mixture was cooled in ice during the addition and blanketed with

nitrogen. When addition was complete (ca. 5 min), stirring was continued at 0° for a further 30 min. Water (200 ml) was then added and the organic phase was separated, washed with 8% sodium bicarbonate (100 ml), dried and concentrated to give the title compound (2.3 g) as a solid, m.p. 115°-118°.

Intermediate 25

5,6-Dihydro-4-[(2-iodophenyl)methylamino]-2(1H)pyridinone

A mixture of 2-iodo-(N-methyl)aniline (1.17 g) and 2,4-dioxopiperidine (565 mg) was heated under a stream of nitrogen for 7 h at 110°-120°. After cooling the reaction mixture was dissolved in methanol and the solution was adsorbed onto FCC silica. Purification by FCC eluting with System A (150:8:1) gave the title compound (1.03 g), m.p. 163°-164°.

Intermediate 26

N,N5-Trimethyl-4-[1,2,3,6-tetrahydro-4-[(2-iodophenyl)-methylamino]-6-oxo-1-pyridinyl]methyl-1Himidazole-1-sulphonamide

A suspension of 5,6-dihydro-4-[(2-iodophenyl)me-25 thylamino]-2(1H)-pyridinone (984 mg) in dry DME (50 ml) was treated with sodium hydride (60% dispersion in oil; 140 mg), and the mixture was stirred under nitrogen for 6 h. 4-(Chloromethyl)-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (832 mg) was then added and 30 the resulting mixture was stirred at 60° overnight. After cooling the reaction mixture was poured into water (100 ml), and the mixture was extracted with ethyl acetate (2×50 ml). The combined, dried organic extracts were concentrated, and the resultant solid was purified by FCC eluting with System A (150:8:1) to give the title compound (712 mg), t.l.c. (System A, 150:8:1) Rf 0.41.

Intermediate 27

N,N,5-Trimethyl-4-[(2,3,4,5-tetrahydro-5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2-yl)methyl]-1H-imidazole-1-sulphonamide

A solution of dimethylsulphamoyl chloride (0.107 ml) in dry dichloromethane was added to a stirred solution of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (0.294 g) and triethylamine (0.2 ml) in dry dichloromethane (30 ml) under nitrogen, and the mixture was heated at reflux for ca. 24 h. After cooling the solution was concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give an oil. This oil was triturated with ether to give a solid which was further purified by slow evaporation from a solution in ethyl acetate to give the title compound (122 mg), m.p. 194°-196°, t.l.c. (System A, 100:8:1) Rf 0.43.

Intermediate 28

Phenylmethyl

5-methyl-4-[(2,3,4,5-tetrahydro-5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2yl)methyl]-1H-imidazole-1-car-boxylate

A solution of benzyl chloroformate (0.28 ml) in dichloromethane (10 ml) was added to a stirred solution of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1Himidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1one (294 mg) and triethylamine (0.4 ml) in dichloromethane (30 ml) at 20° under nitrogen, and the mixture was stirred overnight. It was then concentrated onto FCC silica

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and purified by FCC eluting with System A (200:8:1) to give the title compound (62 mg), t.l.c. (System A, 100:8:1) Rf 0.50.

Intermediate 29

2,3,4,5-Tetrahydro-2-[[1-(methoxymethyl)-5-methyl-1H-imidazol-4-yl]-methyl]-5-methyl-1H-pyrido[4,3-b]indol-1-one and

2,3,4,5-Tetrahydro-2-[[1-(methoxymethyl)-4-methyl-1H-imidazol-5yl]methyl]-5-methyl-1H-pyrido[4,3-b]indol-1-one

A solution of chloromethyl methyl ether (0.26 ml) in dichloromethanc (10 ml) was added to a stirred solution of 2,3,4,5-tetrahydro-5-methyl-2[(5-methyl-1H-15 imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (500 mg) and triethylamine (0.49 ml) in dichloromethane (50 ml) at 20° under nitrogen, and the solution was stirred for 4 days. It was then partitioned between dichlormethane (50 ml) and sodium bicarbonate solution (2×50 ml). The organic extract was dried, concentrated onto FCC silica, and then purified by FCC elution with System A (100.8:1) to give the title compounds (139 mg). A portion of the title compound (64 mg) was taken up in hot ethyl acetate and purified by slow evaporation from ethyl acetate to give the title compounds.

Analysis Found: C67.3; H,6.9; N,16.5; C₁₉H₂₂N₄O₂ requires C,67.4; H,6.6; N,16.6%.

Intermediate 30

2,3,4,5-Tetrahydro-5-methyl-2-[(4-methyloxazol-5-yl)methyl]-1H-pyrido[4,3-b]-indol-1-one

Sodium hydride (60% dispersion in oil; 600 mg) was added to a stirred suspension of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (1.5 g) in dry DME (150 ml) and then the mixture was stirred at 60° for 5 h under nitrogen. 5-Chloromethyl-4-methyloxazole (1.2 g) was added and the mixture was stirred overnight. A further quantity of sodium hydride (60% dispersion in oil; 600 mg) was added and the mixture was stirred at 60° for 4 h, then cautiously treated with water (100 ml). The mixture was extracted with dichloromethane containing methanol (ca. 1%) (3×100 ml) and the combined extracts were evaporated. The residue was purified by FCC eluting with System A (100:8:1) to give the title compound (300 mg) as a solid, t.l.c. (System A, 100:8:1) Rf 0.4.

Intermediate 31

N-[(1-Methyl-1H-indol-2-yl)ethyl]trifluoroacetamide

A solution of 2-(1-methyl-1H-indol-2-yl)ethanamine (3.48 g) in dry dichloromethane (50 ml) containing triethylamine (2.53 g) was cooled in an ice bath, and trifluoroacetic anhydride (5.25 g) was added dropwise over 15 min. The mixture was then allowed to warm to room temperature and stirred for an additional 3 h. After this time the reaction mixture was poured into water (100 ml), the organic phase was separated, and the aqueous phase was washed with dichloromethane (2×50 ml). The combined, dried organic extracts were concentrated onto FCC silica and purification by FCC eluting with ether gave the title compound (4.2 g) as a solid. A 65 sample of this compound was further purified by slow evaporation from a solution in dichloromethane, m.p. 124°-126°.

Intermediate 32

N,N,5-Trimethyl-4-[[(1-methyl-1H-indol-2-yl)-N-tri-fluoroacetylamino]-ethyl]imidazole-1-sulphonamide

A solution of N-[(1-methyl-1H-indol-2-yl)ethyl]tri-fluoroacetamide (2.7 g) in dry DMF (100 ml) was treated with sodium hydride (60% dispersion in oil; 480 mg), and the mixture was stirred at room temperature for 30 min. 4-(Chloromethyl)-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (2.37 g) was then added and the mixture was stirred at room temperature overnight. After this time the reaction mixture was poured into water (500 ml) and the resulting suspension was extracted with ethyl acetate (2×100 ml). The combined organic extracts were washed with water (5×250 ml), dried and adsorbed onto FCC silica. Purification by FCC eluting with System A (150.8:1) gave the title compound (1.9 g), m.p. 156°-158°.

Intermediate 33

4-[[((1-Methyl-1H-indol-2-yl)ethyl]amino]methyl]-N,N,5-trimethyl-1H -imidazole-1-sulphonamide

A mixture of N,N,5-trimethyl-4[[(1-methyl-1H-indol-2-yl)-N-trifluoro-acetylamino]ethyl]imidazole-1-sulphonamide (260 mg), methanol (10 ml) and saturated aqueous potassium carbonate solution (5 ml) was heated to 60° for 1.5 h. After cooling the mixture was poured into water (50 ml) and the mixture was extracted with ethyl acetate (2×50 ml). The combined, dried organic extracts were concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the title compound (143 mg) as an oil, t.l.c. (System A, 100:8:1) Rf 0.51.

Intermediate 34

4-[[[(3-Iodo-1-methyl-1H-indol-2-yl)ethyl]trifluoroacetylamino]-methyl]-N,N,5-trimethyl-1Himidazole-1-sulphonamide

A solution of 4-[[[(1-methyl-1H-indol-2-yl)ethyl-] jamino]methyl]-N,N,5-trimethyl-1H-imidazole-1-sul-phonamide (471 mg) in methanol (25 ml) containing potassium carbonate (138 mg) was treated with a solution of iodine (254 mg) and potassium iodide (166 mg) in water (30 ml) over 30 min. When addition was complete the reaction mixture was stirred for a further 2 h. After this time additional methanol was removed in vacuo and the resulting suspension was extracted with ethyl acetate (3×25 ml). The combined organic extracts were concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the title compound (367 mg), m.p. 141°-143°.

Intermediate 35

4-[[(3-Iodo-1-methyl-1H-indol-2-yl)ethyl]amino]methyl]-N,N,5-trimethyl-1H-imidazole-1-sulphonamide

4-[[[(3-Iodo-1-methyl-1H-indol-2-yl)ethyl]tri-fluoroacetylamino]-methyl]-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (199 mg) was deprotected according to the method described in Intermediate 33 to give the title compound (50 mg) as an oil, t.l.c. (System A, 150:8:1) Rf 0.51.

EXAMPLE 1

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

mixture of 2,3,4,5-tetrahydro-5-methyl-1Hpyrido[4,3-b]indol-1-one (0.6 g) and ca. 78% sodium hydride dispersion in mineral oil (0.109 g) in dry DMF (15 ml) was stirred under nitrogen at 50° until hydrogen evolution ceased (ca. 1.5 h). The mixture was cooled to 10 40° and a solution of 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (1.12 g) in dry THF (15 ml) was added. The reaction was then stirred at 40° for 3 h, at 20° for 16 h and a further portion of 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (1.12 15 g) in dry THF (15 ml) was added. The resulting mixture was heated at 40° for 3 h, quenched with water (20 ml) and acetic acid (20 ml), and heated at 100° for 2 h. The mixture was then concentrated in vacuo to ca. 60 ml, 20 diluted with 1M hydrochloric acid (40 ml) and washed with ethyl acetate $(3 \times 50 \text{ ml})$. The organic phase was discarded and the acidic aqueous phase was basified (pH9) with potassium carbonate and extracted with ethyl acetate: ethanol (20:1, 3×100 ml). The extracts 25 were combined, dried and evaporated to give a brown gum (ca. 1 g). This gum was adsorbed onto silica and purified by FCC eluting with System A (100:8:1) to give a pale brown solid (0.8 g) m.p. 238°-240° (decomp). This solid was dissolved in a mixture of hot ethanol and 30 methanol (1:1; 100 ml) and treated with an ethanolic solution of maleic acid (318 g). The resulting solution was concentrated to ca. 20 ml and diluted with dry diethyl ether (ca. 8 ml) to precipitate the title compound 35 5-Ethyl-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-(0.75 g) as an off-white solid, m.p. 160°-162°.

Found: C,61.6; H,5.5; N,13.6; Analysis C₁₇H₁₈N₄O.C₄H₄O₄ requires C,61.5; H,5.4; N,13.8%.

EXAMPLE 2

3.4.5.6-Tetrahydro-6-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-azepino[4,3-b]indol-1(2H)-one maleate

3,4,5,6-Tetrahydro-6-methylazepino[4,3-b]indol-1-(2H)-one (0.64 g) was treated with sodium hydride (ca. 45 75-80% dispersion in oil; 0.108 g) and was then stirred with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole as described in Example 1. The reaction mixture was then poured into water (300 ml) and extracted with dichloromethane (4×250 ml). The com- 50 bined, dried organic extracts were evaporated to give a semi-solid (ca. 1.8 g) which was purified by FCC eluting with System A (200:8:1) to give a gum (0.7 g). The gum (0.7 g) was dissolved in a mixture of acetic acid, THF and water (1:1:1; ca. 70 ml) and heated on a steam 55 bath for 1 h. Work-up as described in Example I gave a gum (0.22 g) which was purified by FCC eluting with System A (200:8:1) to give a solid (0.11 g). Maleate formation gave a gum which was dried in vacuo to give a foam which was triturated with a mixture of ether and ethanol (50:1; ca. 25 ml) to give the title compound (0.145 g) as a solid, m.p. 132°-133°.

H-N.m.r. indicated 0.39 mol of ethanol present. Water Analysis Found 0.583% w/w=0.14 mol H₂O. 65 Analysis Found: C,61.4; H,5.7; N,12.6; C18H20N4O. C4H4O4.0.39EtOH. 0.14 H2O requires C,61.4; H,6.0; N,12.6%.

EXAMPLE 3

2,3,4,5-Tetrahydro-2[(5-methyl-1H-imidazol-4-yl)methyl]-5-[(phenylmethoxy)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

A suspension of 2,3,4,5-tctrahydro-5-[(phenylmethoxy)methyl]-1H-pyrido[4,3-b]indol-1-one (920 mg) in dry DME (75 ml) was treated with sodium hydride (60% dispersion in oil; 180 mg) under nitrogen and the reaction mixture was stirred at 60° for 6 h.

4-(Chloromethyl)-5-methyl-1-(triphenylmethyl)-1Himidazole (1.11 g) was then added and the mixture was stirred at 60' overnight. Acetic acid (10 ml), water (10 ml) and THF (10 ml) were then added and the resulting solution was heated at reflux for 6 h. After cooling, 2N sodium hydroxide (100 ml) was added and the resulting suspension was extracted with dichloromethane (3 × 100 ml). The combined, dried organic extracts were adsorbed onto FCC silica, and FCC eluting with System A (150:8:1) gave the free base of the title compound (1.08 g) as a foam. A small amount of this compound (200 mg) was dissolved in methanol (30 ml) and the resulting solution was treated with maleic acid (58 mg). The solution was heated for 10 min., cooled, and dry ether was added to precipitate the title compound (170 mg), m.p. 165°-168°.

Water Analysis Found 0.22% w/w=0.06 mol H₂O. Analysis Found: C,64.5; H,5.6; N,10.7; C24H24N4O.C4 H₄O₄, 0.06 H₂O requires C,65.0; H,5.5; N,10.8%.

Examples 4 to 7 were prepared in a similar manner to Example 3.

EXAMPLE 4

yl)methyl]-1H-pyrido[4,3-b]indol-1-one malcate

5-Ethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one (500 mg) was treated with sodium hydride (60% dispersion in oil; 138 mg) and was then stirred with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1Himidazole (927.5 mg) to give the free base of the title compound (320 mg) as a solid. Maleate formation gave the title compound (380 mg), m.p. 175.5°-177°.

C,62.1; H,5.7; Found: C₁₈H₂₀N₄O.C₄H₄O₄ requires C,62.2; H,5.7; N,13.2%.

EXAMPLE 5

2,3,4,5-Tetrahydro-5-(1-methylethyl)-2-[(5-methyl-1Himidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

2.3.4.5-Tetrahydro-5-(1-methylethyl)-1H-pyrido[4,3b]indol-1-one (228 mg) was treated with sodium hydride (60% dispersion in oil; 60 mg) and was then stirred with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (371 mg) to give the free base of the title compound (180 mg) as a solid. Maleate formation gave the title compound (172 mg), m.p. 203'-205'.

N,12.6: Found: C,62.6; H,6.0; Analysis C₁₉H₂₂N₄O.C₄H₄O₄ requires C,63.0; H,6.0; N,12.8%.

EXAMPLE 6

2,3,4,5-Tetrahydro-5-(phenylmethyl)-2-[(5-methyl-1Himidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one maleate monohydrate

2,3,4,5-Tetrahydro-5-(phenylmethyl)-1H-pyrido[4,3blindol-1-one (960 mg) was treated with sodium hydride (73% dispersion in oil; 132 mg) and was then

stirred with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (1.3 g). The free base of the title compound (571 mg) was obtained as a solid by FCC eluting with System A (175:8:1). Maleate formation gave the title compound (420 mg), m.p. 198°-200°, t.l.c. 5 (System A, 100:8:1) Rf 0.3.

EXAMPLE 7

5-(Cyclopentylmethyl)-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one 10 maleate

5-(Cyclopentylmethyl)-2,3,4,5-tetrahydro-1Hpyrido[4,3-b]indol-1-one (200 mg) was treated with sodium hydride (60% dispersion in oil; 60 mg) and was then stirred with 4-(chloromethyl)-5-methyl-1-(tri-15 phenylmethyl)-1H-imidazole (280 mg). The free base of the title compound was obtained as a solid (96 mg) by FCC eluting with System A (200:8:1). Maleate formation gave the title compound (60 mg), m.p. 81°-83', t.l.c. (System A, 100:8:1) Rf 0.20.

EXAMPLE 8

2,3,4,5-Tetrahydro-5-methyl-2-[(5-propyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

Sodium hydride (60% dispersion in oil; 25 mg) was added to a stirred suspension of 2,3,4,5-tetrahydro-5methyl-1H-pyrido[4,3-b]indol-1-one (124 mg) in dry DME (5 ml) under nitrogen. The mixture was heated at 50° for 7 h and then treated with a solution of 4-(chloromethyl)-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide (165 mg) in dry DME (3 ml) and stirring was continued at 50° for 20 h. 2N Hydrochloric acid (5 ml) was added and the solution was heated at reflux for 6 h. The solution was poured into 8% sodium 35 bicarbonate solution (50 ml) and extracted with dichloromethane (3×25 ml). The combined, dried organic extracts were evaporated to give a solid (200 mg) which was purified by FCC eluting with System A (200:10:1) to give the free base of the title compound (58 mg) as a 40 solid. This was dissolved in warm absolute ethanol (5 ml) and treated with a solution of maleic acid (21 mg) in ethanol (0.5 ml). The solvent was removed in vacuo and the residue was crystallised from ethanol:ether to give the title compound (58 mg), m.p. 137°-138°.

N,12.4; Found: C,62.7; H,5.9; C₁₉H₂₂N₄O.C₄H₄O₄ requires C,63.0; H,6.0; N,12.8%.

EXAMPLE 9

2,3,4,5-Tetrahydro-N,N-dimethyl-2-[(5-methyl-1Himidazol-4-yl)methyl]-1-oxo-5H-pyrido[4,3-b]indole-5carboxamide maleate

A solution of 2,3,4,5-tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1Hpyrido[4,3-b]indol-1-one (261 mg) in dry DMF (25 ml) 55 was treated with sodium hydride (60% dispersion in oil; 30 mg) and the mixture was stirred at room temperature under nitrogen for 15 min. N,N-Dimethylcarbamoyl chloride (1M solution in DMF; 1 ml) was then added and the solution was stirred at room temperature for an 60 1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one additional 15 min. Water (1 ml) was cautiously added, and the reaction mixture was then poured into water (100 ml). The resulting mixture was extracted with ethyl acetate (2×50 ml) and the combined organic extracts were washed with water (2×100 ml) and concen-65 trated to give an oil. The oil was dissolved in a mixture of water (10 ml), glacial acetic acid (10 ml) and THF (10 ml) and the solution was heated at reflux for 1.5 h. After

cooling the solution was basified by addition of 2N sodium hydroxide (100 ml), and the resulting mixture was extracted with ethyl acetate (2×75 ml). The combined, dried organic extracts were adsorbed onto FCC silica and the free base of the title compound (110 mg) was obtained by FCC eluting with System A (100:8:1) as a solid. This was dissolved in dry methanol (10 ml) and heated with maleic acid (36 mg) on a steam bath for

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itate the title compound (105 mg), m.p. 161°-163°. Water Analysis Found 1.85% w/w≡0.49 mol H₂O. Analysis Found: C,5.78; H,5.4; N,14.3; C19H21N5O2.C4 H₄O₄. 0.49 H₂O requires C,68.0; H,5.5; N,14.7%.

5 min. On cooling, dry ether (3 ml) was added to precip-

Examples 10, 11 and 12 were prepared in a similar manner to Example 9 unless otherwise stated.

EXAMPLE 10

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(methylsulphonly)-1H -pyrido[4,3-b]indol-1-one maleate

2,3,4,5-Tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one (261 mg) was treated with sodium hydride (60% dispersion in oil; 30 mg) and was then stirred with methanesulphonyl chloride (1M solution in dry DMF; 1 ml) for 45 min. Deprotection, work-up and purification gave the free base of the title compound (60 mg) as a solid. Maleate formation gave the title compound (57 mg), m.p. 152°-155°.

Analysis C.53.2: H.4.7: Found: C₁₇H₁₈N₄O₃S.C₄H₄O₄ requires C,53.2; H,4.7; N,11.8%.

EXAMPLE 11

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propynyl)-1H-pyrido[4,3-b]indol-1-one maleate

A suspension of 2,3,4,5-tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1Hpyrido[4,3-b]indol-1-one (522 mg) and potassium carbonate (276 mg) in dry acetone (75 ml) was treated with propargyl bromide (1M solution in acetone; 2 ml) and the mixture was heated at reflux overnight. After cooling, excess acetone was removed in vacuo to give an oil which was partitioned between water (100 ml) and ethyl acetate (100 ml). The aqueous phase was washed with ethyl acetate (50 ml) and the combined organic extracts were concentrated in vacuo. Deprotection, work-up and purification gave the free base of the title compound (100 mg) as a solid. Maleate formation gave the title compound (89 mg), m.p. 202°-205°, t.l.c. (System A, 100:8:1) Rf 0.29.

EXAMPLE 12

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propenyl)-1H-pyrido[4,3-b]indol-1-one maleate

2,3,4,5-Tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-(1.0 g) was treated with sodium hydride (60% dispersion in oil; 114 mg) and was then stirred with allyl bromide (460 mg) for 1 h. Deprotection, work-up and purification gave the free base of the title compound (380 mg) as a solid. Maleate formation gave the title compound (160 mg), t.l.c. (System A, 100:8:1) Rf 0.3.

C,63.2; H,5.5; N,12.5; Analysis Found: C₁₉H₂₀N₄O.C₄H₄O₄ requires C,63.3; H,5.5; N,12.8%.

EXAMPLE 13

5-Cyclopentyl-2,3,4,5-tetrahydro-2[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

A solution of 2,3,4,5-tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1Hpyrido[4,3-b]indol-1-one (523 mg) in dry DMF (30 ml) was treated with sodium hydride (60% dispersion in oil; 46 mg) and stirred for 15 min. at 21° under nitrogen. Cyclopentyl bromide (298 mg) was then added dropwise, and the mixture was stirred for 1 h and then heated at reflux for 4 h. The solution was left at 21° for 2 days, and then treated with a mixture of acetic acid (7 15 ml), water (7 ml) and THF (8 ml). The resulting solution was heated at reflux for 4 h, then basified with 2N sodium hydroxide and extracted with dichloromethane (3×25 ml). The combined extracts were washed with water (2×50 ml), concentrated in vacuo and purified by 20 FCC eluting with System A (100:8:1) to give the free base of the title compound (42 mg) as a solid. Maleate formation gave the title compound (38 mg), m.p. 180° (dccomp.), t.l.c. (System A, 100:8:1) Rf 0.3.

EXAMPLE 14

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-propyl-1H-pyrido[4,3-b]indol-1-one maleate

A solution of 2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propyl)-1H-pyrido[4,3-b]indol-1-one (248 mg) in a mixture of ethanol (20 ml) and 2N hydrochloric acid (0.5 ml) was hydrogenated at room temperature and atmospheric pressure over a pre-reduced 10% palladium oxide on carbon catalyst (50% aqueous paste; 50 mg). The mixture was filtered and evaporated in vacuo. The residue was basified with 2N sodium hydroxide (10 ml) and extracted with dichloromethane (3×20 ml). The combined organic extracts were washed with water (30 ml) and evaporated to give the free base of the title compound (258 mg) as a solid. Maleate formation gave the title compound 345 mg), t.l.c. (System A, 100:8:1) Rf 0.4.

Water Analysis Found 1.13% w/w=0.28 mol H₂O. Analysis Found: C,62.1; H,5.9; N,12.5; C₁₉H₂₂N₄O.C₄. H₄O₄ 0.28 H₂O requires C,62.2; H,6.0; N,12.6%.

EXAMPLE 15

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido-[4,3-b]indol-1-one maleate

A suspension of 2,3,4,5-tetrahydro-2-[(5-methyl-1Himidazol-4-yl)-methyl]-5-[phenyl(methoxymethyl)]-1Hpyrido[4,3-b]indol-1-one (400 mg) in ethanol (20 ml) and glacial acetic acid (5 ml) was hydrogenated overnight at room temperature and atmospheric pressure 55 over a pre-reduced 10% palladium oxide on carbon catalyst (50% aqueous paste; 100 mg). The reaction mixture was filtered and the residue was washed with ethanol (100 ml). The filtrate was concentrated in vacuo to give an oil, to which was added 2N sodium hydrox- 60 ide (50 ml). The resulting suspension was extracted with dichloromethane (2×50 ml) and the combined, dried organic extracts were evaporated to give a solid. This was purified by FCC eluting with System A (75:8:1) to give the free base of the title compound as a solid (240 65 mg) which was then dissolved in dry methanol (50 ml). Maleate formation gave the title compound (261 mg), t.l.c. (System A, 75:8:1) Rf 0.2

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Analysis Found: C,60.3; H,5.2; N,13.8 C₁₆H₁₆N₄O.C₄H₄O₄ requires C,60.6; H,5.1; N,14.1%.

EXAMPLE 16

2,3,4,5-Tetrahydro-5-methyl-2-[(I,5-dimethyl-1Himidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

Sodium hydride (73% dispersion in oil; 40 mg) was added to a stirred suspension of 2,3,4,5-tetrahydro-5methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1Hpyrido[4,3-b]indol-1-one (300 mg) in dry DMF (3 ml) under nitrogen. After 30 min. the suspension was cooled to 0° and iodomethane (0.076 ml) was added dropwise. The mixture was allowed to reach room temperature, stirred for 1.5 h, then poured into water (30 ml) and extracted with dichloromethane (3×15 ml). The combined, dried organic extracts were evaporated to give an oil (ca. 545 mg) which was purified by FCC eluting with System A (200:8:1) to give a solid (95 mg). A portion of this material (90 mg) was dissolved in absolute ethanol (3 ml) and treated with a solution of maleic acid (35 mg) in absolute ethanol (1 ml). The solvent was removed in vacuo and the residue was triturated with 25 dry ether $(3 \times 5 \text{ ml})$ to give the title compound (122 mg), m.p. 178°-180°.

Analysis Found: C,62.1; H,5.7; N,13.1; C₁₈H₂₀N₄O.C₄H₄O₄ requires C,62.3; H,5.7; N,13.2%.

EXAMPLE 17

2,3,4,5-Tetrahydro-2-[(1H-imidazol-4-yl)methyl]-5methyl-1H-pyrido[4,3-b]indol-1-one dimaleate

A solution of 2,3,4,5-tetrahydro-5-methyl-2-[[(1-(tri-phenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one (0.22 g) in a mixture of acetic acid, THF and water (1:1:1; 10 ml) was heated on a steam bath for 30 min. The suspension so obtained was diluted with 1M hydrochloric acid (20 ml) and washed with ethyl acetate (3×20 ml). The acidic aqueous phase was basified with solid sodium carbonate and extracted with dichloromethane:methanol (9:1; 3×20 ml). The combined, dried organic extracts were evaporated to give a foam which was dissolved in methanol (5 ml) and treated with a solution of maleic acid (0.15 g) in methanol (5 ml). The clear solution was evaporated to give a gum which on trituration with ether afforded the title compound (0.17 g) as a solid, m.p. 117°-118°.

Analysis Found: C,56.1; H,4.3; N,10.5; C₁₆H₁₆N₄O.2C₄H₄O₄ requires C,56.2; H,4.7; N,10.9%.

EXAMPLE 18

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (1.00 g) was suspended in ethanol (40 ml) and concentrated hydrochloric acid (1.00 ml) was added. The mixture was warmed to 40° and charcoal (0.25 g) was added. The resulting suspension was stirred and warmed for 5 min. and then filtered. The filtrate was evaporated in vacuo to ca. 20 ml and was allowed to cool to 20°. Ether (40 ml) was added with stirring over 5 min., and the mixture was stored at 4° overnight. The resulting precipitate was filtered off, washed with ether (2×10 ml), dried in vacuo at room temperature for 2 h

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and then at 70° for 7 h to give the title compound (0.95 g), m.p. 288°-291°.

Analysis Found: C,61.4; H,5.8; N,16.7; Cl, 10.7; C₁₇H₁₈N₄O.HCl requires C,61.7; H,5.8; N,16.9; Cl, 10.7%.

EXAMPLE 19

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one sulphate

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (0.81 g) was suspended in absolute ethanol (6 ml) and was warmed at 50° with concentrated sulphuric acid (0.15 ml). More ethanol (4 ml) was added and the mixture was stirred with charcoal (0.1 g). The suspension was then filtered and the collected solid was washed with ethanol (ca. 3 ml). The resulting filtrate was stirred for ca. 1 h at room temperature, tert-butyl methyl ether (10 ml) was added slowly and the mixture was stirred for 20 min. The precipitate was filtered off, washed with ethanol:tert-butyl methyl ether (1:1;6 ml), then with tert-butyl methyl ether (6 ml), and dried in vacuo at 40° for 4 days to give the title compound (0.4 g), m.p. 205°-209°.

Analysis Found: C,49.5; H,5.6; N, 13.5; S,8.4; C₁₇H₁₈N₄O. 1.1H₂SO₄ requires C,49.9; H,5.4; N, 13.3; S, 8.4%.

EXAMPLE 20

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A suspension of 2,3,4,5-tetrahydro-5-methyl-1Hpyrido[4,3-b]indol-1-one (400 mg) in dry DME (50 ml) 35 was treated with sodium hydride (60% dispersion in oil; 100 mg), and the mixture was stirred at 60° under nitrogen for 6 h. 4-(Chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (474 mg) was added and the reaction mixture was stirred at 60° under nitrogen over- 40 night. 2N Hydrochloric acid (10 ml) and water (10 ml) were then added, and the mixture was heated at reflux for 6 h. After cooling, the mixture was basified with 2N sodium hydroxide and the resulting mixture was extracted with ethyl acetate (2×50 ml). The combined, 45 dried organic extracts were concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the title compound (352 mg) as a solid, t.l.c. (System A, 100:8:1) Rf 0.28. 1H-N.m.r.: 82.2 (3H,s), 3.04 (2H,t), 3.62 (2H,t), 3.72 (3H,s), 4.53 (2H,s), 50 7.1-7.28 (2H,m), 7.43 (1H,s), 7.47-7.55 (1H,dd), 7.94-8.03 (1H,dd).

EXAMPLE 21

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-55 4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A mixture of 2,5-dihydro-5-methyl-2-[[(5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one (50 mg) and 10% palladium oxide on carbon catalyst (50% 60 aqueous paste; 25 mg) in absolute ethanol (10 ml) was heated at 80° in a hydrogen atmosphere at 80 p.s.i. for 24 h. The suspension was filtered and the filtrate was evaporated to give an oil (49 mg) which was purified by short path column chromatography on silica gel (Merck 65 7739) eluting with System A (150:10:1) to give the title compound (8 mg) as a solid, t.l.c. (System A, 150:10:1) Rf 0.36. The ¹H-n.m.r. data obtained for this material

were consistent with those obtained for the product of Example 20.

EXAMPLE 22

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of 2,3,4,5-tetrahydro-2[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1Hpyrido[4,3-b]indol-1-one (261 mg) in dry DMF (25 ml) was treated with sodium hydride (60% dispersion in oil; 30 mg) and the mixture was stirred at room temperature under nitrogen for 15 min. Iodomethane (0.5M solution in DMF; 2 ml) was then added and stirring was continued for a further 15 min. The reaction mixture was then poured into water (100 ml) and the resulting suspension was extracted with ethyl acetate (2×50 ml). The combined organic extracts were washed with water (2×100 ml), dried and concentrated to give a solid. This was dissolved in a mixture of water (10 ml), THF (10 ml) and glacial acetic acid (10 ml) and heated at reflux for 2 h. After cooling, residual THF was removed in vacuo and the remaining solution was basified (to pH14) by 25 addition of 2N sodium hydroxide. The resulting suspension was extracted with ethyl acetate (2 × 50 ml) and the combined, dried organic extracts were concentrated onto silica (Merck 7385). FCC eluting with System A (100:8:1) gave the title compound (81 mg) as a solid. The ¹H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 23

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

5,6-Dihydro-1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone (20.0 mg) was dissolved in 98% sulphuric acid (1 ml) and the solution was stirred at 25° for 5 min. The mixture was cautiously poured into 8% aqueous sodium bicarbonate solution (60 ml) and extracted with 10% methanol:dichloromethane (2×60 ml). The combined, dried organic extracts were evaporated in vacuo to leave an oil which was purified by FCC eluting with System A (100:8:1) to give the title compound (13.5 mg) as a solid. The ¹H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 24

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of N,N,5-trimethyl[-4-[1,2,3,6-tetrahydro-4-[(2-iodophenyl)methylamino]-6-oxo-1-pyridinyl]methyl]-1H-imidazole-1-sulphonamide (264 mg) in a mixture of dioxane and acetonitrile (2:1; 200 ml) containing tricthylamine (2 ml) was irradiated in a pyrex immersion well with a medium pressure 125 W mercury lamp at room temperature for 24 h. The reaction mixture was then concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the title compound (87 mg) as a solid. The ¹H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 25

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of N,N,5-trimethyl-4-[(2,3,4,5-tetrahydro-5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2-yl)methyl]-1H-imidazole-1-sulphonamide (86 mg) in 2N hydrochloric acid (10 ml) and absolute ethanol (2 ml) was heated at 100°-110° for 4 h. The reaction mixture was then cooled and 2N sodium hydroxide (50 ml) was 10 2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazoladded. The resulting solution was extracted with dichloromethane (2×50 ml) and the combined, dried organic extracts were concentrated onto FCC silica and purified by FCC eluting with System A (100:8:1) to give a solid (36 mg). This was taken up in hot ethyl acetate 15 and purified by slow evaporation to give the title compound (12 mg). The ¹H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 26

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of N,N,5-trimethyl-4-[(2,3,4,5-tetrahydro-25 5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2-yl)methyl]-1H-imidazole-1-sulphonamide (401 mg) in a mixture of dioxane (150 ml) and acetonitrile (150 ml) containing triethylamine (1 ml) was irradiated at room temperature with a medium pressure mercury lamp for 24 h. The 30 reaction mixture was then concentrated in vacuo onto FCC silica and purified by FCC eluting with System A (100:8:1) to give the title compound (203 mg) as a solid. The IH-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of 35 Example 20.

EXAMPLE 27

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of phenylmethyl 5-methyl-4-[(2,3,4,5-tetrahydro-5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2yl)methyl]-1H-imidazole-1-carboxylate (134 mg) in a mixture of absolute ethanol and 2N hydrochloric acid (2:1; 30 ml) was heated on a steam bath for 15 min. After 45 cooling, the solution was concentrated in vacuo to ca. 20 ml and diluted with water (40 ml). The mixture was then washed with ethyl acetate (2×40 ml) and the acidic aqueous layer was basified with potassium carbonate solution. The solution was then extracted with 50 ethyl acetate (3×50 ml) and the combined, dried organic extracts, were concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give a solid. This was dissolved in hot methanol and triturated with ether to give the title compound (69 mg). 55 reaction mixture was poured into 2N hydrochloric acid The ¹H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 28

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of 2,3,4,5-tetrahydro-2-[[1-(methoxymethyl)-5-methyl-1H-imidazol-4-yl]methyl]-5-methyl-1Hpyrido[4,3-b]indol-1-one and 2,3,4,5-tetrahydro-2-[[1- 65 the protected derivative of the title compound (21 mg) (methoxymethyl)-4-methyl-1H-imidazol-5-yl]methyl]-5-methyl-1H-pyrido[4,3-b]indol-1-one (34 mg) in 49% hydrobromic acid (2 ml) was heated on a steam bath for

ca. 3 h. After cooling, the reaction mixture was basified by addition of potassium carbonate solution and extracted with ethyl acetate (3×50 ml). The combined, dried organic extracts were concentrated in vacuo to give the title compound (6 mg) as a solid. The ¹H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 29

4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

mixture of 2,3,4,5-tetrahydro-5-methyl-2-[(4methyloxazol-5-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (100 mg) in formamide (20 ml) was heated at 180° for 24 h. The mixture was then cooled, diluted with water (100 ml) and extracted with dichloromethane (3×100 ml). The combined organic extracts were concentrated in vacuo and the residue was purified by FCC 20 eluting with System A (100:8:1) to give the title compound (40 mg) as a solid. The H-n.m.r. and t.l.c. data for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 30

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of 4-[[[(1-methyl-1H-indol-2-yl)ethyl-]amino]methyl]-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (140 mg) in dry dichloromethane (15 ml) was cooled to 5° and the mixture was stirred under nitrogen while phosgene (12% w/w solution in toluene; 1 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, aluminium trichloride (60 mg) was powdered and added, and stirring was continued overnight. After this time methanol (1 ml) was added and the reaction mixture was adsorbed onto FCC silica and purified by FCC cluting with System A (150:8:1) to give the protected derivative of the title compound (42 mg), as a solid, identical (by t.l.c. and m.p.) to the product of Intermediate 27. Deprotection as described in either of Examples 25 or 26 gives the title compound.

EXAMPLE 31

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A mixture of 4-[[(3-iodo-1-methyl-1H-indol-2-yl)ethyl]amino]methyl]-N,N,5-trimethyl-1H-imidazole-1sulphonamide (70 mg), triphenylphosphine (52 mg) and palladium acetate (22 mg) in tri-n-butylamine (5 ml) and dry THF (1 ml) was heated under an atmosphere of carbon monoxide at 120° for 1 h. After cooling the (50 ml) and the resulting mixture was extracted with ethyl acetate (2×50 ml; discarded). The acidic solution was then basified with 2N potassium carbonate and the resulting basic suspension was extracted with ethyl 60 acetate (2×50 ml). The combined, dried organic extracts were concentrated in vacuo to give an oil and residual tri-n-butylamine was removed by distillation to leave a solid. This was adsorbed onto FCC silica and purified by FCC eluting with System A (150:8:1) to give as a solid, identical (by t.Lc. and m.p.) to the product of Intermediate 27. Deprotection as described in either of Examples 25 or 26 gives the title compound.

EXAMPLE 32

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

5,6-Dihydro-1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone (60 mg) was dissolved in glacial acetic acid (4 ml). Anhydrous zinc chloride (600 mg) was added, and the mixture was heated at 85° for 1.5 h. The cooled mixture was 10 poured into 8% aqueous sodium bicarbonate solution (100 ml) and extracted with ethyl acetate:methanol (10:1) (2×100 ml). The combined, dried organic extracts were evaporated in vacuo to leave a solid which was purified by FCC eluting with System A (100:8:1) to give the title compound (26 mg). The ¹H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

formulations according to the invention, containing 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-1-yl)methyl]-1H-pyrido[4,3-b]indol-1-one as the active ingredient. Physiologically acceptable salts and/or solvates of this compound, and other compounds of for- 25 mula (I) and their physiologically acceptable salts and-/or solvates may be formulated in a similar manner.

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such 30 as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tab- 35 lets may be sugar coated.

Direct Compression		
Tablet	mg/tablet	44
Active Ingredient	0.50	_
Calcium Hydrogen Phosphate BP*	87.25	
Croscarmellose Sodium NF	1.80	
Magnesium Stearate BP	0.45	
Compression weight	90.00	4

of a grade sultable for direct compression.

The active ingredient is passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate. croscarmellose sodium and magnesium stearate. The 50 excipients. The mix is filled into size No. 2 hard gelatin resultant mix is compressed into tablets using a Manesty F3tablet machine fitted with 5.5 mm, flat bevelled edge punches.

		55
Sub-Lingual Tablet	mg/tablet	
Active Ingredient	0.5	
Compressible Sugar NF	64.5	
Magnesium Stearate BP	0.5	
Compression Weight	65.0	60

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of other strengths may be 65 prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

Wet Granula	tion
Conventional Tablet	mg/tablet
Active Ingredient	0.5
Lactose BP	153.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
Compression Weight	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using 7 mm diameter punches.

Tablets of other strengths may be prepared by alter-The following examples illustrate pharmaceutical 20 ing the ratio of active ingredient to lactose or the compression weight and using punches to suit.

Sub-Lingual Tables	mg/tablet
Active Ingredient	0.5
Mannitol BP	58.5
Hydroxypropylmethylcellulose	5.0
Magnesium Stearate BP	1.0
Compression Weight	65.0

The active ingredient is sieved through a suitable sieve and blended with the mannitol and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended into tablets using suitable punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to mannitol or the compression weight and punches to suit.

_	tablet	mg/tablet
	Active Ingredient	0.5
	*Starch 1500	98.5
	Magnesium Stearate BP	1.0
,	Fill Weight	100.0

'a form of directly compressible starch.

The active ingredient is sieved and blended with the capsules using suitabled machinery. Other doses may be prepared by altering the fill weight an if necessary changing the capsule size to suit.

SYRUP

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup			mg/5 ml dose
Active Ingredient			0.5
Sucrose BP			2750.0
Glycerine BP			500.0
Buffer			
Flavour	1		
Colour	ì		as required
Preservative	,		
Purified Water BP		to	5.0 ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. 5 The syrup is clarified by filtration.

B. Storose-Free			mg/5 ml dose
Active Ingredient			0.5
Hydroxypropylmethylcellulose USP			
(viscosity type 4000)			22.5
Buffer	\		
Flavour	1		
Colour	Ş		as required
Preservative			
Sweetener)		
Purified Water EP		to	5.0 ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solu- 20 tion containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

INJECTION FOR INTRAVENOUS ADMINISTRATION			_
	mg/	ml .	
Active Ingredient	0.05	0.5	
Sodium Chloride BP	as required	as required	
Water for Injection BP to	1.0 ml	1.0 ml	

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate 35 solution of the active ingredient. Alternatively, suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave 40 using one of the acceptable cycles. Alternatively, the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

METERED DOSE I	RESSURISED AERO	OSOL	
Suspension Aerosol	mg/metered dose	Per can	
Active Ingredient micronised	0.050	12.0 mg	- 5
Oleic Acid BP	0.020	4.80 mg	3
Tricklorofluoromethane BP	23.64	5.67 g	
Dichlorodifluoromethane BP	61.25	14.70 g	

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The oleic acid is mixed with the trichlorofluoromethane at a temperature of 10°-15° C. and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering 85 mg of suspension are crimped 60 onto the cans and the dichlorodifluoromethane is pressure filled into the cans through the valves.

Solution Aerosol		
	mg/metered dose	Per can
Active Ingredient Ethanol BP	0.05 7.500	12.0 mg 1.80 g

-continued

Solution Aerosol		
	Per can	
Trichlorofluoromethane BP	18.875	4.53 g
Dichlorodifluoromethane BP	48.525	11.65 g

Oleic acid BP, on a suitable surfactant e.g. Span 85 (sorbitan trioleate) may also be included).

The active ingredient is dissolved in the ethanol together with the oleic acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoromethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

Inhalation Cartrid	lges
	mg/cartridge
Active Ingredient (micronised)	0.05
Lactose BP to	25. 0 0

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder in-30

SUPPOSITO	DRY
Active Ingredient	0.5 mg
*Witepsol H15 to	1.0 g

*Witepsol H15 is a proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient is prepared in the molten Witepsol and filled, using suitable machinery, into Ig size suppository moulds.

We claim:

45

1. A compound of formula (I)

$$\bigcap_{\substack{\text{in}\\ \text{in}\\ \text{R}^1}}^{\text{O}} \bigcap_{\text{Im}}^{\text{Im}}$$

wherein Im represents an imidazolyl group of the for-

and R1 represents a hydrogen atom or a group selected from C1.6alkyl, C3.6alkenyl, C3.10alkynyl, C3.7cycloalkyl, C3.7cycloalkyl C1-4alkyl, phenyl, phenylC1-3alkyl, 65 phenylmethoxymethyl, phenoxyethyl phenoxymethyl;

one of the groups represented by R2, R3 and R4 is a hydrogen atom or a C1.6alkyl, C3.7cycloalkyl, C3. 6alkenyl, phenyl or phenylC1.3alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1.6}alkyl group;

n represents 2 or 3;

or a physiologically acceptable salt or solvate thereof. 5

- 2. A compound according to claim 1 in which R¹ represents a C₁₋₄alkyl, C₃₋₄alkynyl, C₅₋₆cycloaklyl, C₅₋₆cycloaklylmethyl, phenylC₁₋₂alkyl, or phenylmethoxymethyl.
- 3. A compound according to claim 1 in which R², R³ 10 and R⁴ each independently represent a hydrogen atom or a C₁₋₃alkyl group.
- 4. A compound according to claim 1 in which R¹ represents a hydrogen atom or a C₁₋₄alkyl, C₃₋₄alkenyl, C₃₋₄alkynyl, C₅₋₆cycloaklyl, C₅₋₆cycloaklylmethyl, phenylC₁₋₂alkyl, or phenylmethoxymethyl, R² represents a hydrogen atom; and R³ and R⁴ each represent a hydrogen atom or a C₁₋₃alkyl group.
- 5. A compound according to claim 1 in which R¹ represents a methyl, n-propyl, prop-2-ynyl, cyclopentyl, cyclopentylmethyl, or benzyl; R² and R³ each represent a hydrogen atom; and R⁴ represents a methyl group.
- 6. A compound according to claim 4 in which n represents 2.
- 7. A compound according to claim 5 in which n represents 2.
- 8. 2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one; or a physiologically acceptable salt or solvate thereof.

9. A compound selected from:

- 2,3,4,5-Tetrahydro-5-(phenylmethyl)-2-[(5-methyl-1Himidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one;
- 5-cyclopentyl-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one;
- 2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-propyl-1H-pyrido[4,3-b]indol-1-one;
- 5-(cyclopentylmethyl)-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indollone;
- 3,4,5,6-tetrahydro-6-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-azepino[4,3-b]indol-1(2H)-one;
- 2,3,4,5-tetrahydro-N,N-dimethyl-2-[(5-mcthyl-1H-imidazol-4-yl)methyl]-1-oxo-5H-pyrido[4,3-b]indole-45 5-carboxamide;
- 2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)meth-yl-5-(2-propynyl)-1H-pyrido[4,3-b]indol-1-one;
- or a physiologically acceptable salt and solvate thereof.
- 10. A compound according to claim 1 in the form of 50 a hydrochloride, hydrobromide, sulphate, alkylsulphonate, arylsulphonate, phosphate, acetate, citrate, succinate, tartrate, fumarate or malente salt.
- 11. The compound of claim 8 in the form of a hydrochloride salt.
- 12. The compound of claim 8 in the form of a maleate salt.
- 13. A pharmaceutical composition which comprises an effective amount of a compound of formula (I) is 2, an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or 60 blindol-1-one hydrochloride. 30. A method according cally acceptable carrier or excipient.
- 14. A pharmaceutical composition according to claim 13 in a form adapted for oral or parenteral administration.
- 15. A pharmaceutical composition according to claim 13 wherein the active ingredient is 2,3,4,5- tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-

- pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.
- 16. A pharmaceutical composition according to claim 13 wherein the active ingredient is 2,3,4,5-tetrahydro-5methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl-1Hpyrido[4,3-b]indol-1-one hydrochloride.
- 17. A method of treating a condition which is ameliorated by antagonism of 5HT₃ receptors which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof to relieve said condition.
- 18. A method according to claim 17 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl15 2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.
 - 19. A method according to claim 17 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.
 - 20. A method according to claim 17 wherein the condition which is ameliorated by antagonism of 5HT₃ receptors is anxiety.
 - 21. A method according to claim 20 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.
 - 22. A method according to claim 20 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.
- 23. A method according to claim 17 wherein the 35 condition which is ameliorated by antagonism of 5HT₃ receptors is schizophrenia.
 - 24. A method according to claim 23 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-
- 40 blindol-1-one or a physiologically acceptable salt or solvate thereof.
 - 25. A method according to claim 23 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.
 - 26. A compound according to claim 1 which is 5-ethyl-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.
 - 27. A method according to claim 17 for the treatment of irritable bowel syndrome.
 - 28. A method according to claim 27 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl-1H-pyrido[4,3-
- 55 b]indol-1-one or a physiologically acceptable salt or solvate thereof.
 - 29. A method according to claim 27 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-blindol-1-one bydrochloride
 - 30. A method according to claim 17 wherein the condition which is ameliorated by antagonism of 5HT₃ receptors is dyspepsia.
- 31. A method according to claim 30 wherein the 65 compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

- 32. A method according to claim 30 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.
- 33. A method according to claim 17 wherein the 5 condition which is ameliorated by antagonism of 5-HT₃ receptors is reflux oesophagitis.
- 34. A method according to claim 33 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-

2[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

35. A method according to claim 33 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

* * * *



EXHIBIT 6

Terminal Disclaimer filed in United States
Patent Application No. 07/741,570
U.S. Patent No. 5,360,800

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
IAN H COATES et al)
Serial Number: 07/741,570	Group Art Unit: 1203
Filed: August 7, 1991) Examiner: Alan L Rotman
For: LACTAM DERIVATIVES)

TERMINAL DISCLAIMER

Honorable Commissioner of Patents and Trademarks Washington, D.C. 20231

Sir:

Your Petitioner, Glaxo Group Limited (henceforth referred to as "Assignee"), having a place of business at Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, England, represents that it is the owner by assignment of the entire right and title to the above-captioned patent application and the invention and improvements therein disclosed for the United States by virtue of an assignment from the inventors, dated August 22, 1988 and recorded at Reel 4993, Frames 723-725, on September 15, 1988.

Assignee, who is also owner of the entire right and title to U.S. patent Number 5,183,820 by assignment recorded at Reel 5773, Frames 178-180 on July 17, 1991, hereby disclaims the terminal part of any patent granted on the above-captioned application which would extend beyond the expiration date of the full statutory term as presently shortened by any terminal disclaimer of U.S. Patent Number 5,183,820, and hereby agrees that any patent so granted on the above-captioned application shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to U.S. Patent Number 5,183,820, this agreement to run with any patent granted on the above-captioned application and to be binding upon the grantee, its successors or assigns. Notwithstanding the above disclaimer, Assignee does not waive any rights available under the provisions of 35 U.S.C. §§ 155 and 156.

Serial Number 07/741,570

Assignee does not disclaim any terminal part of any patent granted on the above-captioned application prior to the expiration date of the full statutory term as present shortened by any terminal disclaimer of U.S. Patent Number 5,183,820 in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. § 1.321(a), has all claims cancelled by a re-examination certificate, or is otherwise terminated prior to the expiration of its statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above. Assignee does not disclaim any terminal part of any patent granted on the above-captioned application resulting from any extension of that patent granted under the provisions of 35 U.S.C. §§ 155, 155(a) and 156.

Documentary evidence which establishes a chain of title of the above-captioned U.S. patent application from the original owner to the Assignee has been reviewed by Assignee and Assignee certifies under 37 C.F.R. §3.73(b) that to the best of Assignee's knowledge and belief, title is in the assignee seeking to take the present action.

I, Alan Hesketh, am empowered to act on behalf of the Assignee, and I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statement and the like so made are punishable by fine, or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-captioned application.

Signed at Greenford, Middlesex, England

this 24th day of February 1994.

GLAXO GROUP LIMITED by their Attorney

Alan Hesketh



EXHIBIT 7

Assignment to Glaxo Group Limited of Application for Letters Patent of United States Patent Application No. 07/691,814

U.S. Patent No. 5,183,820

Express Mail Label No. EM484297842US I, RICHARD GRAHAM ROSSER, of the City of London, Notary Public duly admitted and sworn practising in the said City,

DO HEREBY CERTIFY AND ATTEST:

THAT the signatures set and subscribed at foot of the hereunto annexed document are genuine, the same having been duly subscribed thereto by IAN HAROLD COATES, ALEXANDER WILLIAM OXFORD, PETER CHARLES NORTH and BARRY JOHN PRICE, whose identities I attest.

IN TESTIMONY WHEREOF I have hereunto set my hand and affixed my Seal of Office in the City of London aforesaid, this twenty-sixth day of June One thousand nine hundred and ninety-one.



39

APOSTILLE

(Hague Convention of 5 October 1961/Convention de La Haye du 5 octobre 1961)

 Country: United Kingdom of Great Britain and Northern Ireland Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document/Le présent acte public

۷.	a été signé par	K-G-BSSER
3.	acting in the capacity of agissant en qualité de	Notary Public
		THE SAID NOTARY PUBLIC

Certified/Attesté

27 JUN 1991

- 5. at London/à Londres
- 6. the/le
- by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs/ par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.
- 8. Number/sous No

G 080288

9. Stamp: timbre:



10. Signature:

For the Secretary of Side / Pour its Secretaire d'Etai

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RECORDED PATENT AND TRADEMARK OFFICE

<u>ASSIGNMENT</u>

JUL 17 1991

For good and valuable considerations, the receipt and sufficiency of which is hereby acknowledged, WE

> Ian Harold COATES Alexander William OXFORD Peter Charles NORTH Barry John PRICE

do hereby sell, assign, convey and set over to our assignees,

Glaxo Group Limited, a British company, Clarges House, 6/12 Clarges Street, London, W1Y 8DH, England.

our entire right, title and interest in and to an invention entitled

Lactam Derivatives

and in and to the application for Letters Patent of the United States thereon, filed 26th April, 1991 as Application Serial No. 07/691,814, to any patent or patents that may issue on said application and invention in the United States of America and foreign countries, to assist in securing which we hereby covenant and agree on behalf of ourselves, our heirs, executors and legal representatives, to execute without further compensation all papers and assignment connected with such patent or application therefor and I do hereby authorise and request the Commissioner of Patents to issue any patents maturing on said US application to our assignee beneficial owner thereof;

IN WITNESS WHEREOF, We have hereunto set our hand and seal this 24th day of June

Ian Harold COATES

Hardd Coakes

Peter Charles NORTH

Alexander William OXFORD

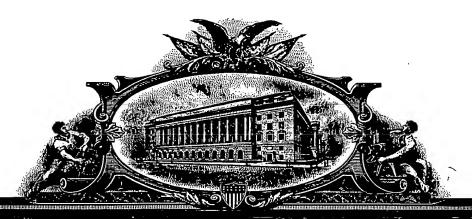
exande William

Barry John PRICE



EXHIBIT 8

Maintenance Fee Statement for U.S. Patent No. 5,360,800



United States Patent and Trademark Office

October 04, 1999

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE **RECORDS OF THIS OFFICE OF:**

MAINTENANCE FEE STATEMENT

SERIAL NUMBER: 07/741,570 FILING DATE: August 07, 1991

> By Authority of the COMMISSIONER OF PATENTS AND TRADEMARKS

Certifying Officer



UNITED STATES DEPARTMENT OF COMMERCE

Patent and Trademark Office

ASSISTANT COMMISSIONER FOR TRADEMARKS 2900 Crystal Drive Arlington, VA 22202-3513

DATE MAILED 09/30/1999

RICHARD E. FICHTER BACON AND THOMAS PTO BOX 76 ARLINGTON VA 22202

In response to your communication of 09/30/1999 concerning the status of payment of maintenance fees due, the following is provided:

Patent Number : 5360800 Application Serial Number : 07/741,570 Application Filing Date : 08/07/1991 Issue Date : 11/01/1994

Status: 8TH YEAR FEE WINDOW OPENS: 11/01/2001

(PTOL-438)



EXHIBITS 9A – 9G

Document Chronology / Due Diligence Logs for IND No. 34,672,
Document Chronology / Due Diligence Logs for IND No. 39,083,
Document Chronology / Due Diligence Logs for IND No. 45,128,
Transcript of Dr. Camilleri's remarks before the Gastrointestinal
Drugs Advisory Committee

Document Chronology / Due Diligence Logs for IND No. 48,487,
Document Chronology / Due Diligence Logs for NDA 21-107, and
Document Chronology / Due Diligence Logs for IND No. 59,496

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_	EXHIBIT 9A	
	Document Chronology / Due Diligence Logs for	
	IND No. 34,672,	
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REGULATORY AFFAIRS

DOCUMENT TRACKING SYSTEM CHRONOLOGY

Page 1 11:23 AM

B. ...

Application: July 34672 GR68755C

DOCS006 23-JAN-96

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29-JUN-90		17-APR-90		11-APR-90			10-APR-90	DOC/ACT DATE
LETTER from PDA to GLAXO	REFERENCE APPLICATION IND 34672	LETTER from FDA to GLAXO	IND DELIVERED 10-APR-90 IND BEGIN WILL BE UP 10-MAY-90	MEMO from GLAXO to GLAXO	PROTOCOL INV# S3B-101 2267	GR68755 IS A POTENT, SELECT STUDIES IN AGE ASSOCIATED N	LETTER from GLAXO to FDA	METHOD OF COMMUNICATION
REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS	REFERENCE SUP#/ ACT# SBR# METHOD OF CO	ACKNOWLEDGEMENT	# ASSIGNED 34672 30 WAITING	INTERNAL COMMUNICATION INTERNAL COMMUNICATION	INVESTIGATOR Kisicki James C	A POTENT, SELECTIVE COMPETITIVE ANTAGONIST AT THE 5-AGE ASSOCIATED MEMORY IMPAIRMENT (AAMI) ARE PLANNED.	ORIGINAL APPLICATION	PROCESS
C M C INCLUSIVE/GENERAL CLINICAL INCLUSIVE/GENERAL PROTOCOL INVESTIGATIONAL DRUG LABELING	OF COMMUNICATION DOC/ACT DATE from GLAXO to FDA 10-APR-90	UPDATE	PERIOD BEFORE CLINICAL TRIALS MAY	FDA REVIEW STATUS UPDATE	•	HE 5-HT3 RECEPTOR SITE. FUTURE	BIOAVAILABLTY/PHARMACOKINETICS PROTOCOL DOSING REGIMEN SAFETY NON-CLINICAL GENERAL PHARMACOLOGY TOXICOLOGY	SUBJECT
2.001-		2.001-					1.001- 1.010	DCR VOL RANGE
 							000	SUP#/ SER#

* 41

FDA REQUESTS ADDITIONAL CMC INFORMATION & SUGGESTS STUDY S3B-101 INCLUDE MORE FREQUENT VITAL SIGNS MONITORING. ALSO CONFIRMS 5.10.90 VERBAL ACCEPTANCE TO INITITATE CLINICAL STUDY.

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Application: IND 34672 GR68755C

23-JAN-96 DOCS006

ACT# 25-JUL-90/ TELECON from FDA to GLAXO 24-JUL-90 DOC/ACT DATE RESPONDING TO GLX REQUEST OF 7.11.90, CSO DECORTE INDICATES CHEMISTRY QUESTIONS OF 6.29.90 WERE SENT IN ERROR & INSTRUCTED GLX NOT TO RESPOND TO QUESTIONS 6,8,9,10,11. GLX INDICATES RESPONSE TO REMAINING QUESTIONS FORTHCOMING. METHOD OF COMMUNICATION PROTOCOL APPLICATION REFERENCE APPLICATION IND 34672 REFERENCE REFERENCE REFERENCE RESPONSE TELECONFERENCE TELECONFERENCE ACT# sup#/ SER# SER# sup#/ PROCESS INVESTIGATOR METHOD OF COMMUNICATION LETTER from FDA to GLAXO METHOD OF COMMUNICATION LETTER from GLAXO to FDA FDA CONSULT/GUIDANCE C M C INCLUSIVE/GENERAL FDA REVIEW STATUS SUBJECT DOC/ACT 29-JUN-90 DOC/ACT 10-APR-90 DATE DATE VOL RANGE 2.001-2.001 SUP#/ SER#

RESPONDING TO 6.29.90 LTR, GLX SUBMITS CMC INFORMATION INCLUDING ADDITIONAL TABLET STRENGTH

SPONSOR COMMITMENT

CLINICAL INCLUSIVE/GENERAL

STUDY REPORT FOREIGN INFORMATION

PROTOCOL

FORMULATION

SPECS/ANALYTICAL METHODS STABILITY

STABILITY

SPECS/ANALYTICAL METHODS METHOD OF MANUFACTURER CONTAINER/CLOSURE SYSTEM

2.001-2.001

INFO AMND:

CLINICAL CLINICAL

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CLINICAL

15-NOV-90 LETTER from GLAXO to FDA

INFO

INFO

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(2MG) & UPDATED D-S STABILITY DATA & ADDITIONAL IDENTITY SPECIFICATION FOR D-S. ADDITIONALLY GLX WITHDRAWS 1MG TABLET STRENGTH. GLX ALSO COMMENTS ON AGENCY REQUEST FOR INCREASED VITAL SIGN MONITORING & CATALOGS CV PARAMETERS TO BE MEASURED DURING NEXT VOLUNTEER PROTOCOL. GLX SUMMARIZES UK SAFETY & TOLERANCE STUDIES FOR FDA & SUBMITS RECHALLENGE STUDY REPORT.

REGULATORY AFFAIRS

DOCUMENT TRACKING SYSTEM CHRONOLOGY

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Application: IND 34672 GR68755C

DOCS006 23-JAN-96

003	4.001-	PROTOCOL	PRTCL AMND: PROTOCOL CHANGE	LETTER from GLAXO to FDA	8 28-FEB-91
			Hunt Thomas L.	S3B-102 2548 S3B-102	
			INVESTIGATOR	PROTOCOL INV#	
		NTEERS) SUBMITTED. CLINICAL DATA TO SUPPORT PROTOCOL PHARMACOKINETIC/YOUNG & ELDERLY/ORAL VS IV), SUMMARY SAFETY & PHARMACOKINETICS/VOLUNTEERS), GPK/90/008 REPORT X 9-1/2DAYS/VOLUNTEERS). NONCLINICAL REPORTS ALSO		NEW PROTOCOL S3B-102 (TOLERANCE/VOLINCLUDES: STUDY REPORT GPK/90/006 REPORT FOR S3B-101 (ASCENDING-DOSE, (PHARMACOKINETCIS/TOLERANCE/4MG BIDINCLUDED AS FINAL REPORTS.	
002	3.001-3.005	POREIGN INFORMATION STUDY REPORT PROTOCOL PRIN-INVESTIGATOR ADD STUDY REPORT TOX: MUTAGENICITY ADME	INFO AMND: CLINICAL INFO AMND: CLINICAL INFO AMND: CLINICAL PRTCL AMND: NEW PROTOCOL PRTCL AMND: NEW PROTOCOL INFO AMND: PHARM/TOXICOLOGY INFO AMND: PHARM/TOXICOLOGY INFO AMND: PHARM/TOXICOLOGY	LETTER from GLAXO to FDA	7 17-JAN-91
			INVESTIGATOR	PROTOCOL INV# GHP8923 GHP8938 GHP9005 S3B-101	
		DOC/ACT DATE LATION DATE to GLAXO 1 to GLAXO 25-JUL-90/ 24-JUL-90	REFERENCE SUP#/ ACT# SER# METHOD OF COMMUNICATION 4 LETTER from FDA to GLAX 5 TELECON from FDA to GLAX	REFERENCE FAPPLICATION IND 34672 IND 34672	
SUP#/ SBR#	DCR VOL RANGE	SUBJECT	PROCESS	METHOD OF COMMUNICATION	DOC/ACT ACT# DATE

PROTOCOL MODIFICATION TO COLLECT HOLTER MONITOR RECORD DURING SCREEN PERIOD BEFORE DAY 1 (BASAELINE).

REGULATORY AFFAIRS

DOCS006 23-JAN-96

Application: IND 34672 GR68755C

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		11 02-			10 04-		9 28-		ACT# DO
		02-MAY-91			04-APR-91/ 03-APR-91		28-MAR-91		DOC/ACT DATE
REFERENCE APPLICATION IND 34672 IND 34672	AS COMMITTED IN 11.15.90 FOR IMPURITIES & RESIDUAL IMPURITIES, WILL ALSO SUI 2) CHROMATOGRAPHS FOR UNDIRESIDUAL SOLVENT IN D-S;	LETTER from GLAXO to FDA	PROTOCOL S3B-102	RMO CRANDALL CONTACTS G	TELECON from FDA to GLAXO	MFG CONTROL# CGS01977	LETTER from GLAXO to FDA	PROTOCOL S3A-102	METHOD OF COMMUNICATION
	1.15.90 RESPONSE 7 RESIDUAL SOLVENT I ALSO SUPPORT SUIT/ FOR UNDEGRADED & I IN D-S; 4) REVISED	JA -	#ANI	GLX TO I	ΧO)A	#ANI	NOI
REFERENCE SUP#/ ACT# SER#	1.15.90 RESPONSE TO FDA 6.29.90 PRESIDUAL SOLVENT DETERMINATIONS. ALSO SUPPORT SUITABILITY OF HPLC FOR UNDEGRADED & DEGRADED SAMPLE! IN D-S; 4) REVISED D-S SPECIFICAT	INFO AMND: CMC RESPONSE	IN	DETERMINE STATUS	REQUESTS/COMMENTS	ADR PROCESS	10-DAY WRITTEN	IN	PRO
O PO COURT	SPEC METH	CMC/MICROBIOLOGY	INVESTIGATOR	OF S3B-102	NTS	ESS	ISR	INVESTIGATOR	PROCESS
OF COMMUNICATION from FDA to GLAXO	TO FDA 6.29.90 LTR, GLX PROVIDES REVISED METHODOLOGY & DA DETERMINATIONS. SPECIFICALLY, 1) HPTLC USED TO CHARACTERIZ FABILITY OF HPLC METHODOLOGY FOR ROUTINE ANALYSIS; DEGRADED SAMPLES; 3)GC METHOD TO REPLACE NMR TO DETERMINE D-S SPECIFICATION FOR SOLVENT LEVEL.	00		STUDY. GLX REPLIES	PROTOCOL	REPORT SUBMISSION CODE DATE I 28-MAR-91	SAPETY		8
DOC/ACT DATE DATE 29-JUN-90	GLX PROVIDES REVISED METHODOLOGY & DATA IFICALLY, 1) HPTLC USED TO CHARACTERIZE GODOLOGY FOR ROUTINE ANALYSIS; GC METHOD TO REPLACE NMR TO DETERMINE FOR SOLVENT LEVEL.	INCLUSIVE/GENERAL		REPLIES STUDY COMPLETED,) I			SUBJECT
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Application: IND 34672 GR68755C

DOCS006 23-JAN-96

DOC/ACT ACT# DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT V	DCR VOL RANGE	SUP#/ SBR#
12 22-MAY-91	LETTER from GLAXO to FDA	ANNUAL REPORT (IND)	INVESTIGATOR BROCHURE CLINICAL DEVEL PROGRAM PROTOCOL CLINICAL STUDY STATUS SAFETY NON-CLINICAL GENERAL	4.001-	006
	REPORT PERIOD COVERS APRIL 19	1990 TO APRIL 1991.			
13 02-JUL-91	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY INFO AMND: PHARM/TOXICOLOGY	SAPETY STUDY REPORT	4.001-	007
	GLX SUMMARIZES FINDINGS RELATED POSITIVE AMES TEST FOR GR68755C	TED TO PRECLINICAL SAFETY STUDIES 55C INTERMEDIATE.	w/COMPOUND, SPECIFICALLY		
	PROTOCOL INV# WPT/90/261 WPT/90/304	INVBSTIGATOR			
14 01-AUG-91/ 31-JUL-91	TELECON from FDA to GLAXO	HOLD ON IND (ENTIRE DRUG PRG)	UPDATE	4.001-	
	CSO DECORTE CALLS TO INFORM (POSITIVE AMES TEST RPT.	TO INFORM GLX THAT FDA WAS PLACING A CLN HOLD ON Γ RPT.	OLD ON GR68755 AS A RESULT OF THE		
	REFERENCE APPLICATION IND 34672	REFERENCE SUP#/ ACT# SER# METHOD OF COMMUNIC	OF COMMUNICATION DOC/ACT from GLAXO to FDA 02-JUL-91		
15 01-NOV-91	LETTER from FDA to GLAXO	GENERAL CORRESPONDENCE	FDA CONSULT/GUIDANCE	4.001-	
	FDA LTR ADDRESSES ISSUES AFFECTING IMPLEMENTATION OF THE "CLINICAN'S OF THE TWO OUTCOME MEASURES THAT THE FDA HAS IDENTIFIED AS ESSENTIAL	FDA LTR ADDRESSES ISSUES AFFECTING IMPLEMENTATION OF THE "CLINICAN'S			

REGULATORY AFFAIRS

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Application: IND 34672 GR68755C

DOCS006 16-SEP-97

,	6.001-	MEETING INFO/DETAILS NON-CLINICAL GENERAL	TELECONFERENCE	TELECON from FDA to GLAXO	20 29-APR-92/ 28-APR-92
		ESS, REVISED SPECS & ANALYTICAL NEW 1mg TABLET FORMULATION. INTENDED TO REPLACE THE PREVIOUS 1mg	NFO. DESCRIBE NEW MFG PROC A ON PREVIOUS FORMULATION & DN FOR USE IN CLN STUDIES,	AMEND TO PROVIDE UPDATED CMC INFO. METHODS. UPDATED STABILITY DATA ON INTRODUCE NEW TABLET FORMULATION FOR TABLET GRANULATION FORMULATION.	
'	6.001-	DP: METHOD OF MANUFACTURER DP: SPECS/ANALYTICAL METHODS DP: STABILITY DP: FORMULATION	INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY	LETTER from GLAXO to FDA	19 19-FEB-92
		SAFETY RPT EMERGED IN PRECLN	FETY REPORT SUBMITTED 02-JUL-91.	SUBMIT FOLLOW-UP INFO TO SAFETY SAFETY STUDIES WITH GR68755C.	
·į	5.001-	SAFETY	ANIMAL ADR INFO AMND: PHARM/TOXICOLOGY	LETTER from GLAXO to FDA	18 10-FEB-92
		THE DISCREPANCY OF ONE SUBJECT	PROVIDE AMENDMENT TO RPT GMH/89/024 WHICH DOCUMENT THE DISDIFFERENT REFERENCE NUMBERS.	AMEND TO PROVIDE AMENDMENT TO RPT GM WITH TWO DIFFERENT REFERENCE NUMBERS	
	4.001-	UPDATE STUDY REPORT	INFO AMND: CLINICAL	LETTER from GLAXO to FDA	17 18-DEC-91
		REPORT SUBMISSION CODE DATE F 04-DEC-91	ADR PROCESS FOLLOWUP TO WRITTEN ADR/ISR	MFG CONTROL# CGS01977	
	4.001- 4.001	SAFETY	FOLLOWUP TO WRITTEN ADR/ISR	LETTER from GLAXO to FDA	16 04-DEC-91
ë	DCR VOL RANGE	SUBJECT	PROCESS	METHOD OF COMMUNICATION	DOC/ACT ACT# DATE
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CSO NIGHSWANDER CALLS TO SCHEDULE TELECONFERENCE FOR 11-MAY-92 TO DISCUSS FDA PRECLN CONCERNWITH COMPOUND FOR INDICATION OF AGE ASSOCIATED MEMORY IMPAIRMENT (AAMI). FDA WILL ALSO

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Application: IND 34672 GR68755C

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	24	•		23		22				21		ACT#	App1:
	06-0CT-92			07-JUL-92		12-MAY-92/ 11-MAY-92				30-APR-92		DOC/ACT DATE	Application: IND
SUBMIT PRELIMINARY INFO FROM FURTHER INVESTIGATIONS OF THE EFFECT OF GREPERFORMED DURING AN ORAL ONCOGENICITY STUDY IN WISTAR RATS 6 A 12 MONTH DOGS.	LETTER from GLAXO to FDA INFO AMND: PHARM/TOXICOLOGY TOXICOLOGY	REFERENCE REFERENCE SUP#/ APPLICATION ACT# SER# METHOD OF COMMUNICATION IND 34672 22 TELECON from GLAXO to FDA	GLX PROVIDES ADDITIONAL PHARMACOLOGY/TOXICOLOGY INFORMATION IN RESPONSE (WPT/91/409)	LETTER from GLAXO to FDA INFO AMND: PHARM/TOXICOLOGY TOXICOLOGY RESPONSE	ON 11-MAY-92 A TELECONFERENCE WAS HELD TO DISCUSS PRECLINICAL ISSUES WIT	TELECON from GLAXO to FDA TELECONFERENCE NON-CLINIC	COVERING PERIOD APRIL, 91 TO APRIL, 92.	REPORT (IND) REPORT (IND)	REPORT (IND) REPORT (IND) DP: REPORT (IND) TAVE	LETTER from GLAXO to FDA ANNUAL REPORT (IND) DD. METHOL	EXPLAIN APPARENT INCONSISTENCY W/THIS COMPOUND IN HANDLING OF THE 2 IND8. ON CLN HOLD & IND 39,083 (SCHIZOPHRENIA) IS NOT.	METHOD OF COMMUNICATION PROCESS	ID 34672 GR68755C
GR68755 ON HEARING NTH ORAL STUDY IN BEAGLE	NON-CLINICAL GENERAL TOXICOLOGY	DOC/ACT DATE 12-MAY-92/ 11-MAY-92	NSE TO FDA REQUEST.	X X	WITH FDA.	NON-CLINICAL GENERAL		CLINICAL STUDY STATUS SAFETY NON-CLINICAL GENERAL	SPECS/ANALYTICAL METHODS FORMULATION PORTICIATION	METHOD OF MANIEACTIBED	B. IND 34,672 (AAMI)	SUBJECT	
	7.001-7.001			6.001-		6.001-				6.001-	. 	DCR VOL RANGE	
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REGULATORY AFFAIRS

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Application: IND 34672 GR68755C

DOCS006 16-SEP-97

DOC/ACT	DOC/ACT METHOD OF COMMUNICATION	DRAC DRAC	SIB IECT	DCR VOT. BANGE	SUP#/
1					
25 04-JUN-93	LETTER from GLAXO to FDA	ANNUAL REPORT (IND) ANNUAL REPORT (IND) ANNUAL REPORT (IND) ANNUAL REPORT (IND)	INVESTIGATOR BROCHURE CLINICAL STUDY STATUS SAFETY NON-CLINICAL GENERAL	7.001- 7.001	015
	COVERING ANNUAL REPORTING	PERIOD.		-	
26 03-DEC-93	LETTER from GLAXO to FDA	10-DAY WRITTEN ISR	SAFETY	7.001-7.001	016
	MFG CONTROL# B0002909	ADR PROCESS 10-DAY WRITTEN ISR	REPORT SUBMISSION CODE DATE I 03-DEC-93		
27 24-JAN-94	LETTER from GLAXO to FDA	10-DAY WRITTEN ISR	SAFETY	7.001-7.001	017
	MFG CONTROL# B0003499	ADR PROCESS 10-DAY WRITTEN ISR	REPORT SUBMISSION CODE DATE I 24-JAN-94		
28 18-FEB-94	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	STUDY REPORT	8.001-	018
	PROVIDE FINAL CLINICAL STUDY	DY REPORT UCP/92/019 (PROTOCOL	S3A-102).		
	PROTOCOL INV# S3A-102	# INVESTIGATOR			
29 25-MAR-94	LETTER from GLAXO to FDA	10-DAY WRITTEN ISR	SAFETY	1	019

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Application: IND 34672 GR68755C

ACT# 31 22-JUL-94 LETTER from FDA to GLAXO 30 09-JUN-94 LETTER from GLAXO to FDA DOC/ACT SUBMIT ANNUAL REPORT SUMARIZING PROGRESS OF INVESTIGATIONS DURING THE INTERVAL APRIL, 93 THROUGH APRIL, 94. ALSO SUBMIT ROST FOR THIS IND TO BE PUT ON INACTIVE STATUS AS NO PATIENTS HAVE BEEN ENTERED INTO CLN TRIALS SINCE 30-JUL-91 AND AT THIS TIME GLX HAS NO PLANS FOR ADDTL DEVELOPMENT ACTIVITY OF THIS COMPOUND. IND PLACED ON INACTIVE STATUS METHOD OF COMMUNICATION REFERENCE APPLICATION IND 39083 CONTROL # B0004015 ADR PROCESS 10-DAY WRITTEN ISR REFERENCE SUP#/
ACT# SER#
17 008 ANNUAL REPORT (IND)
ANNUAL REPORT (IND)
INACTIVATES IND INACTIVATES IND PROCESS METHOD OF COMMUNICATION LETTER from GLAXO to FDA REPORT CODE I SAFETY NON-CLINICAL GENERAL UPDATE ADMINISTRATIVE SUBMISSION DATE 25-MAR-94 SUBJECT DOC/ACT DATE 08-JUN-94 VOL RANGE SER# 020

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Regulatory Affairs CARDS

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Chronology

Application: IND Date Range: All 34672; GR68755C (alosetron) Tablets

34672

ALH42326 19-Nov-1999

Date Communication Type
10-Apr-1990 Glaxo Wellcome Correspondence Document Type
Initial Investigational New Drug Application Document Subtype Serial / Supp #

09-Jun-1994 Glaxo Wellcome Correspondence 22-Jul-1994 Food and Drug Administration Correspondence 34672 IND 34,672; GR68755C (alosetron) Tablets Acknowledgement Request to Inactivate IND

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Acknowledgement

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Application: IND 39083 GR68755C

SUP#/ SER#	000	
DCR VOL RANGE	1.001-	
SUBJECT	C M C INCLUSIVE/GENERAL C M C INCLUSIVE/GENERAL INVESTIGATOR BROCHURE CLINICAL DEVEL PROGRAM PROTOCOL PRIN-INVESTIGATOR ADD PATIENT POPULATION STUDY REPORT MONITOR PHARMACOLOGY TOXICOLOGY TOXICOLOGY TOXIC REPRO/TERATOGENICITY ADME	
PROCESS	INCORPORATION BY REFERENCE ORIGINAL APPLICATION	
METHOD OF COMMUNICATION		
DOC/ACT DATE	1 11-MAR-92	
ACT#		

SUBMIT NEW IND TO CONDUCT CLN STUDIES IN SCHIZOPHRENIA, ALSO SUBMIT MOST RECENT SUBMISSION OF CMC DATA TO IND 34,672 WHICH INCLUDES FORMULATION INFO FOR CLN SUPPLIES TO BE USED IN CLN STUDY PROPOSED IN THIS IND. NOTE STUDY MONITOR AS POLLY SANDERSON, Ph.D AND JOE DEVEAUGH-GEISS, M.D. AS SAFETY MONITOR.

DOC/ACT DATE 10-APR-90	
METHOD OF COMMUNICATION LETTER from GLAXO to FDA	or prbert phen vin J.
METHOD	INVESTIGATOR Meltzer Herbert Marder Stephen Miller Marvin J.
SUP#/ SER# 000	HXXX
REFERENCE ACT# 1	
E 10N 2	INV# 4666 4825 4826
REFERENCE APPLICATION IND 34672	PROTOCOL S3B-201 S3B-201 S3B-201 S3B-201

SCHIZOPHRENIA IND DELIVERED TO FDA & IND NUMBER ASSIGNED.

2 16-MAR-92 LETTER from FDA to GLAXO

ACKNOWLEDGEMENT

UPDATE

UPDATE

INTERNAL COMMUNICATION

MEMO from GLAXO to GLAXO

3 13-MAR-92

AFFAIRS REGULATORY

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Application: IND 39083	ID 39083 GR68755C		•	
DOC/ACT ACT# DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR SUP#/
	RECEIPT OF NEW IND ACKNOWLE	EDGED, IND # ASSIGNED, DATE OF RECEIPT NOTED AS 12-MAR-92	EIPT NOTED AS 12-MAR-92.	
	REFERENCE APPLICATION IND 39083	REFERENCE SUP#/ ACT# SER# METHOD OF COMM 1 000 LETTER from GL	OF COMMUNICATION DATE Trom GLAXO to FDA 11-MAR-92	
4 13-APR-92/ 09-APR-92	TELECON from FDA to GLAXO	REQUEST8/COMMENTS	FDA REVIEW STATUS	
	CSO HIGGINS CALLS TO COMMUNI SCHIZOPHRENIA.	NICATE FDA'S DECISION ON RVW OF NEW	W IND IN TREATMENT OF	
	REFERENCE APPLICATION IND 39083	REFERENCE SUP#/ ACT# SER# METHOD OF COMMUNICATION 1 000 LETTER from GLAXO to FD	DOC/ACT OF COMMUNICATION DATE from GLAXO to FDA 11-MAR-92	
5 13-MAY-92	LETTER from GLAXO to FDA	REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS	MEETING INFO/DETAILS CLINICAL DEVEL PROGRAM PROTOCOL	001
6 21-MAY-92	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	PROTOCOL	
	CSO HIGGINS CALLS CONCERNING DONE IN PTCL S3B-201. PREVIC WILL AGAIN AMEND PTCL WITH E	NG PREVIOUS DISCUSSION REGARDING NUMBER OF IOUSLY COMMUNICATED TOTAL WAS NOT WHAT FDA FDA DESIRED CHANGES.	UMBER OF ECGS WHICH WERE TO BE WHAT FDA HAD INTENDED AND GLX	_
	PROTOCOL INV# S3B-201	INVESTIGATOR		
8 29-MAY-92	LETTER from GLAXO to FDA	PRTCL AMND: PROTOCOL CHANGE	PROTOCOL	000

REGULATORY AFFAIRS

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SUP#/ SER#

Application: IND 39083 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PRC	PROCESS	SUBJECT	VOL	DCR VOL RANGE
		AMEND (#1)TO ADD ECGS FOR PTS ON STUDY DAYS 8, 36 & 56 IN ADDTN TO 21 & 49 FROM ORIG PTCL, (#2)MINOR CHANGE IN TERMINOLOGY & (#3)ADDS ECGS FOR EACH PT ON STUDY DAYS 15 & 43 TO BRING TOTAL NUMBER OF ECGS DONE FOR EACH PT DURING CONDUCT OF STUDY TO EIGHT PER ROST OF FDA ON 21-MAY-92.	s on study days 8 DGY & (#3)Adds EC R EACH PT DURING	, 36 & 56 IN ADDIN GG FOR EACH PT ON CONDUCT OF STUDY P	GS FOR PTS ON STUDY DAYS 8, 36 & 56 IN ADDTN TO 21 & 49 FROM ORIG PTCL TERMINOLOGY & (#3)ADDS ECGS FOR EACH PT ON STUDY DAYS 15 & 43 TO BRING BOONE FOR EACH PT DURING CONDUCT OF STUDY TO EIGHT PER ROST OF FDA ON	IG PTCL, FO BRING FDA ON	
		PROTOCOL INV#	I	INVESTIGATOR			
7	09-JUN-92	FAX from FDA to GLAXO	REQUESTS/COMMENTS		FDA REVIEW STATUS	 	
		FDA COMPLETES RVW OF ORIG APPLICATION AND PTCL S3B-201 MAY BEGIN WITECG'S & ONLY 12 PTS ENROLLED AT THIS TIME. DATA FROM THIS STUDY WILL CONCURRENCE REC'D BEFORE FURTHER SCHIZOPHRENIA STUDIES MAY PROCEED. TO IMPROVE SAFETY OF APPLICATION & NOTE PRECLN CONCERNS FROM INVESTI	PLICATION AND PTC AT THIS TIME. DA THER SCHIZOPHRENI FION & NOTE PRECI	L S3B-201 MAY BEGI TA FROM THIS STUDY A STUDIES MAY PROC N CONCERNS FROM IN	PF ORIG APPLICATION AND PTCL S3B-201 MAY BEGIN WITH MODIFICATIONS CONTROLLED AT THIS TIME. DATA FROM THIS STUDY WILL BE RVW'D & FDA BEFORE FURTHER SCHIZOPHRENIA STUDIES MAY PROCEED. NOTE COMMENTS & PROPLICATION & NOTE PRECLN CONCERNS FROM INVESTIGATOR'S BROCHURE.	S OF ADDTL A & REQUESTS RE.	
		REFERENCE APPLICATION IND 39083	REFERENCE SUP#/ ACT# SER# 1 000	METHOD OF COMMUNICATION LETTER from GLAXO to FDA	DOC/ACT CATION DATE to FDA 11-MAR-	DOC/ACT DATE 11-MAR-92	
6	07-JUL-92	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY INCORPORATION BY REFERENCE RESPONSE		TOXICOLOGY TOXICOLOGY TOXICOLOGY		
		GLX PROVIDES PHARMACOLOGY AND TOXICOLOGY INFORMATION IN RESPONSE TO FDA REQUEST. (WPI/91/409) REPORT FILED ONLY WITH IND 34672, SERIAL #013, AND INCORPORATED BY IND 39083, SERIAL #003.	O TOXICOLOGY INFO NLY WITH IND 3467	INFORMATION IN RESPONSE TO FDA REQUEST. 34672, SERIAL #013, AND INCORPORATED BY		REFERENCE TO	
		REFERENCE APPLICATION IND 34672 IND 39083	REFERENCE SUP#/ ACT# SER# 23 013	METHOD OF COMMUNICATION LETTER from GLAXO to FDA FAX from FDA to GLAXO	æ	DOC/ACT DATE 07-JUL-92 09-JUN-92	

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FDA CONSULT/GUIDANCE

TELECONFERENCE

10 10-AUG-92 TELECON from GLAXO to FDA

REGULATORY AFFAIRS

Application: IND 39083 GR68755C

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DCR SUP#/ VOL RANGE SER#					400		005	
SUBJECT	APPROPRIATE EFFICACY SCALES FOR USE IN STUDY OF ACUTE EXACERBATION	FDA CONSULT/GUIDANCE PROTOCOL	STUDY IS A DOULBE-BLIND AND GLX DOES NOT WISH TO BREAK BLIND, IT FDA ALLOW GLX TO ENROLLMENT AT FDA ALLOW GLX TO ENROLL A 13TH PATIENT TO INSURE THAT WE HAVE 12 S WHEN WE SUBMIT THE DATA PKG TO FDA FOR RVW.		NON-CLINICAL GENERAL TOXICOLOGY NON-CLINICAL GENERAL	SUBMIT PRELIMINARY INFO FROM FURTHER INVESTIGATIONS OF THE EFFECT OF GR68755 ON HEARING PERFORMED DURING AN ORAL ONCOGENICITY STUDY IN WISTAR RATS & A 12 MONTH ORAL STUDY IN BEAGLE DOGS. File Note: Attachments filed with IND 34,672, Serial #014, Doc Date 06-Oct-92 and incorporated by reference to this IND.	CLINICAL INCLUSIVE/GENERAL	PER FDA REQUEST OF 09-JUN-92. GLX ONTINUE OUR EARLY PHASE II
PROCESS	ROPRIATE EFFICACY SCALES FOR US	TELECONFERENCE TELECONFERENCE	SPEAK W/CSO HIGGINS REGARDING PTCL VIOLATOR DROPOUT FOR S3B-201. FDA HAS LIMITED ENROLLMENT IN STUDY TO 12 PTS. SINCE STUDY IS A DOULBE-BLIND AND GLX DOES NOT WISH TO BREAK BLIND, THEREFORE GLX PROPOSES THAT FDA ALLOW GLX TO ENROLL A 13TH PATIENT TO INSURE THAT WE HAVE 1 PATIENTS EXPOSED TO GR68755 WHEN WE SUBMIT THE DATA PKG TO FDA FOR RVW.	INVESTIGATOR	INFO AMND: PHARM/TOXICOLOGY INFO AMND: PHARM/TOXICOLOGY INCORPORATION BY REFERENCE	SUBMIT PRELIMINARY INFO FROM FURTHER INVESTIGATIONS OF THE EFFECT OF GR68755 ON HEARING PERFORMED DURING AN ORAL ONCOGENICITY STUDY IN WISTAR RATS & A 12 MONTH ORAL STUDY IN BOGS. File Note: Attachments filed with IND 34,672, Serial #014, Doc Date 06-Oct-92 a incorporated by reference to this IND.	INFO AMND: CLINICAL	SUBMIT INTERIM SAFETY RESULTS FROM 13 PATIENTS FROM S2B-201 PER FDA REQUEST OF 09-JUN-92. SEEKS FDA APPROVAL TO ENROLL THE REMAINING 24 PATIENTS AND CONTINUE OUR EARLY PHASE II DEVELOPMENT PROGRAM.
METHOD OF COMMUNICATION	CONTACT DR LAUGHREN ABOUT APP OF SCHIZOPHRENIA.	TELECON from GLAXO to FDA	SPEAK W/CSO HIGGINS REGARDING IN STUDY TO 12 PTS. SINCE STUTHEREFORE GLX PROPOSES THAT F PATIENTS EXPOSED TO GR68755 W	PROTOCOL INV# S3B-201	LETTER from GLAXO to FDA	SUBMIT PRELIMINARY INFO FROM FURTHER INVESTIGATIONS OF PERFORMED DURING AN ORAL ONCOGENICITY STUDY IN WISTAR DOGS. File Note: Attachments filed with IND 34,672, incorporated by reference to this IND.	LETTER from GLAXO to FDA	SUBMIT INTERIM SAFETY RESULTS SEEKS FDA APPROVAL TO ENROLL DEVELOPMENT PROGRAM.
DOC/ACT DATE		11 21-AUG-92			12 06-0CT-92		14-JAN-93	
ACT#		11			12		13	

FDA REVIEW STATUS

RESPONSE

14 03-FEB-93 LETTER from FDA to GLAXO RESPONSE

INVESTIGATOR

I NV#

PROTOCOL S3B-201

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Application: IND 39083 GR68755C

PROCESS SUBJECT: DAC/ACT DAC/ACT	Application: IND 39083	ron: T	ND 39083 GR68755C					
FOR COMPLETES RYW OF SUBMISSION AND CONCLUDE THAT IT IS REASONABLY SAFE FOR THE ENROLLAMENT OF THE REMAINING 24 PATIENTS IN FTCL 53B-201. REPERENCE APPLICATION ANNIAL REPORT (IND) ANDIAL REPORT	1	YACT VTE	METHOD OF COMMUNICATION	PROC	ESS	SUBJECT	· DCR VOL RANGE	SUP#/ SER#
REPERENCE REFERENCE SUP#/ ANNUAL REPORT (IND) CLINICAL DEVEL PROCRAM ANNUAL REPORT (IND) CLINICAL GENERAL ANNUAL REPORT (IND) CLINICAL STUDY STATUS ANNUAL REPORT (IND) CLINICAL STUDY STATUS ANNUAL REPORT (IND) CLINICAL GENERAL COVERING PERIOD MARCH, 1392 TO MARCH, 1993. 18-FBB-94 LETTER from GLAXO to FDA GENERAL CORRESPONDENCE STUDY REPORT STATUS GENERAL CORRESPONDENCE STUDY REPORT GENERAL CORRESPONDENCE STUDY REPORT STUDY REPORT STUDY REPORT STUDY REPORT STUDY REPORT THE TIME OF THE COMPONDA AND NO PATIENTS HAVE BERETY ANNUAL REPORT (IND) SAFETY NON-CLINICAL GENERAL THE STUDY REPORT STUDY REPORT THE ANNUAL REPORT (IND) SAFETY NON-CLINICAL GENERAL THE STUDY REPORT THE STUDY REPORT STUDY REPORT THE STUDY STUDY THE STUDY STUDY STUDY STUDY STUDY THE STUDY ST			COMPLETES RVW OF SUBMISS REMAINING 24 PATIENTS IN	ION AND CONCLUDE T PTCL 83B-201.	HAT IT IS REASON	ABLY SAFE FOR THE ENROLLMENT O	Eu	
12-MAY-93 LETTER from GLAXO to FDA ANNUAL REPORT (IND) INVESTIGATOR ERCCGURE ANNUAL REPORT (IND) CLINICAL DEVEL PROGRAM ANNUAL REPORT (IND) CLINICAL DEVEL PROGRAM ANNUAL REPORT (IND) STRTUG S					METHOD OF COMMUN LETTER from GLAX	ď		
18-FEB-94 LETTER from GLAXO to FDA GENERAL CORRESPONDENCE STUDY REPORT 18-FEB-94 LETTER from GLAXO to FDA GENERAL CORRESPONDENCE STUDY REPORT 18-FEB-94 LETTER from GLAXO to FDA GENERAL CORRESPONDENCE STUDY REPORT 19-FEB-94 LETTER from GLAXO to FDA GENERAL CORRESPONDENCE STUDY REPORT 19-FEB-94 LETTER from GLAXO to FDA GENERAL (IND) SAFETY 19-FEB-94 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-94 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-94 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-94 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-95 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-95 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-96 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA ANNUAL REPORT (IND) SAFETY 108-JUN-97 LETTER from GLAXO TO FDA AN	15 12-M	IAY-93		REPORT (REPORT (REPORT (REPORT)		TOR BR DEVEL STUDY		900
PROVIDE FINAL STUDY REPORT UCP/92/019 (PROTOCOL S3A-102). File Note: The attachments to this submission are filed to IND 34,672, Serial #018, ONLY. Also this submission was sent to the FDA, but no copies were sent to the DCR. The FDA sent us back a copy. PROTOCOL INV# INVESTIGATOR INVESTIGATOR SAFETY BROTOCOL INV# INVESTIGATOR INVOICED SAFETY OB-JUN-94 LETTER from GLAXO to FDA ANNUAL REPORT (IND) SAFETY ANNUAL REPORT (IND) NON-CLINICAL GENERAL INACTIVATES IND INACTIVATES IND UPDATE SUMMARY OF PROCRESS OF INVESTIGATIONS DURING INTERVAL WARCH, 1993 THROUGH WARCH, 1994. ALSO ROST THAT THIS IND BE PUT ON INACTIVE STATUS. THERE ARE NO PLANS FOR ADDIL DEVELOPMENT ACTIVITY OF THIS COMPOUND AND NO PATIENTS HAVE BEEN ENTERED INTO CLN TRIALS UNDER THIS IND SINCE FEB, 93. ALSO NOTE THAT IND 34,672 WILL BE INACTIVATED AT THE TIME OF 1TS ANNUAL RPT.								
PROVIDE FINAL STUDY REPORT UCP/92/019 (PROTOCOL S3A-102). File Note: The attachments to this submission are filed to IND 34,672, Serial #018, ONLY. Also this submission was sent to the PDA. The FDA sent us back a copy. PROTOCOL INV# INVESTIGATOR S3A-102 S3A-102 INVESTIGATOR SAFETY ANNUAL REPORT (IND) SAFETY ANNUAL REPORT (IND) SUMMARY OF PROGRESS OF INVESTIGATIONS DURING INTERVAL MARCH, 1993 THROUGH MARCH, 1994. ALSO SUMMARY OF PROGRESS OF INVESTIGATIONS DURING INTERVAL MARCH, 1993 THROUGH MARCH, 1994. ALSO ROST THAT THIS IND BE PUT ON INACTIVE STATUS. THERE ARE NO PLANS FOR ADDIL DEVELOPMENT ACTIVITY OF THIS COMPOUND AND NO PATIENTS HAVE BEEN ENTERED INTO CLIN TRIALS UNDER THIS IND SINCE FEB, 93. ALSO NOTE THAT IND 34,672 WILL BE INACTIVATED AT THE TIME OF ITS ANNUAL RPT.	16 18-FI	EB-94	LETTER from GLAXO to FDA	GENERAL CORRESP			! ! ! ! !	007
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Chronology

Application:

45128; GR68755 Tablets treatment of Carcinoid Diarrhea

Transfer of Ownership Document Subtype

Serial / Supp #

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Date Range: All

23-Mar-1994 Date

Communication Type
Glaxo Wellcome Correspondence General Correspondence Document Type

General Correspondence: Letter of Authorization for reference of a Sponsor/Investigator IND

22-Apr-1994

Correspondence

Initial Investigational New Drug Application

0000

IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea

Initial Investigational New Drug Application Serial No.: 0000

28-Apr-1994 Food and Drug Administration Correspondence Acknowledgement

IND # Assigned

IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea

Acknowledgement: IND # Assigned

09-Aug-1994

Food and Drug Administration Correspondence

Comment/Information Request

Clinical

IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea

Comment/Information Request: Clinical

22-Sep-1994

Correspondence

Response to FDA Request/Comment Protocol Amendment: Change in Protocol

Clinical Clinical

0001

Protocol Amendment: Change in Protocol, Clinical IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea

Serial No.: 0001 Response to FDA Request/Comment: Clinical

Application: IND 45128; GR68755 Tablets treatment of Carcinoid Diarrhea Date Range: All	ALH42326 Reg ory Affairs CARDS Chronology
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28-Apr-1995	Food and Drug Administration Telephone Comment/Information Request	Nonclinical	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea GW contacted in requards to non-clinical rat studies (two year rat & mouse oncology studies and 12 month rat study)		
01-May-1995	Correspondence Information Amendment: Clinical	Safety	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Information Amendment: Clinical Serial No.: 0006		000
01-May-1995	Glaxo Wellcome Correspondence Response to FDA Request/Comment	Nonclinical	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Response to FDA Request/Comment: Nonclinical		
02-May-1995	Food and Drug Administration Telephone Comment/Information Request	Clinical	

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10-May-1995 Food and Drug Administration Correspondence Co	Date Communication Type
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IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea

Comment/Information Request: Clinical

07-Aug-1995	·	12-May-1995
Correspondence	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Protocol Amendment: Change in Protocol Serial No.: 0007	Correspondence
Protocol Amendment: New Investigator	Carcinoid Diarrhea	Protocol Amendment: Change in Protocol
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Serial No.: 0008 Protocol Amendment: New Investigator IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea

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IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea	Солгезропденсе
Carcinoid Diarrhea	Annual Report
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Annual Report Serial No.: 0009

06-Mar-1996 Correspondence 10-Day ADR Report 0010

Serial No.: 0010 IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea 10-Day ADR Report

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Date Range: Application: ₽IN

45128; GR68755 Tablets treatment of Carcinoid Diarrhea

09-Aug-1996 Date Communication Type Correspondence Annual Report Document Type Document Subtype Serial / Supp #

Request to Withdraw

0011

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Request to Withdraw Serial No.: 0011 Annual Report IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea

24-Nov-1997 Food and Drug Administration Correspondence Comment/Information Request IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Comment/Information Request

Clinical

IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Acknowledgement: Withdrawal

23-Dec-1997

Food and Drug Administration Correspondence

Acknowledgement

Withdrawal

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EXHIBIT 9D	
Transcript of Dr. Camilleri's remarks before the Gastrointestinal Drugs Advisory Committee	

VRDEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

Tuesday, November 16, 1999 9:00 a.m.

Holiday Inn 2 Montgomery Village Avenue Gaithersburg, Maryland

COMMITTEE MEMBERS PRESENT:

STEPHEN D. HANAUER, M.D., Chairman

ROSEMARY BERARDI, Pharm. D.

GEORGE D. FERRY, M.D.

NANCY L. GELLER, Ph.D.

LOREN LAINE, M.D.

JOANNE A. WILSON, M.D.

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PROCEEDINGS

CHAIRMAN HANAUER: I'd like to welcome you to this morning's meeting. It's obviously going to be an important Advisory Committee meeting, probably precedent-setting, depending upon the--well, in any event, on the outcome of the Committee's thinking process regarding this.

My name is Steve Hanauer. I'm from the University of Chicago, and I'm the Chairman of the GI Drugs Advisory Committee. To begin with, I'd like to have an introduction of those of us at the table. Perhaps we'll start on this end with Dr. Senior, introducing ourselves to the audience.

DR. SENIOR: I'm John Senior. I'm a GI medical reviewer at the FDA.

DR. HOUN: I'm Florence Houn. I'm the Office Director for the Office of Drug Evaluation III at FDA.

DR. TALARICO: I'm Lilia Talarico. I'm the Director of the Division of GI and Coagulation Drug Products.

DR. WALD: I'm Arnold Wald. I'm from the University of Pittsburgh Medical Center.

DR. BERARDI: I'm Rosemary Berardi and I'm from the College of Pharmacy at the University of Michigan, and I'm the consumer representative to this Committee.

DR. LAINE: I'm Loren Laine and I'm from USC Medical School, in Los Angeles, gastroenterology.

DR. WILSON: I'm Joanne Wilson. I'm at Duke University Medical Center, gastroenterology.

MS. STANDAERT: I'm Joan Standaert, the Executive Secretary of the Committee.

DR. FERRY: I'm George Ferry, pediatric gastroenterology, from Baylor College of Medicine, in Houston.

DR. GELLER: I'm Nancy Geller. I'm Director of the Office of Biostatistics Research at the National Heart, Lung, and Blood Institute, in Bethesda.

DR. RACZKOWSKI: To my left will be Dr. Robert
Prizont, who is a medical reviewer from the Division of
Gastrointestinal Drug Products. I am Dr. Victor Raczkowski,
the Deputy Office Director in the Office of Drug Evaluation
III.

DR. GALLO-TORRES: I'm Dr. Hugo Gallo-Torres. I am the Medical Team Leader of the reviewing division, the Division of Gastrointestinal and Coagulation Drug Products.

CHAIRMAN HANAUER: And at this point, Joan

Standaert is going to read a statement regarding conflict of interest.

MS. STANDAERT: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it is has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 U.S.C. 208(b), full waivers have been granted to Dr. Loren A. Laine and Dr. George D. Ferry which permit them to participate in all official matters concerning Lotronex. A copy of these waivers may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A-30 of the Parklawn Building. We would also like to disclose for the record that Dr. William M. Steinberg will be excluded from participating in all matters pertaining to Glaxo Wellcome's Lotronex.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Arnold Wald would like to disclose for the record that he was an investigator on alosetron, but not the principal investigator. He also has a grant from Glaxo on a matter unrelated to alosetron.

In the event that the discussions involve any

other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

That concludes the statement for this meeting.

CHAIRMAN HANAUER: Anyone else want to comment regarding that?

[No response.]

CHAIRMAN HANAUER: Okay. For each of these

Committee meetings, there is an opportunity for the public to make any comments, and at this point we've been notified that there are two individuals who represent the International Foundation for Functional Gastrointestinal Disorders who would like to speak.

I would like to invite Nancy Norton to make the initial comments.

MS. NORTON: Thank you. Good morning, Members of the Committee. Thank you for the opportunity to appear before you today. I am the founder and President of the International Foundation for Functional Gastrointestinal Disorders and the current Chairman of the Digestive Disease

Thank you.

CHAIRMAN HANAUER: The next speaker is Dr. Camilleri, from the Mayo Clinic.

DR. CAMILLERI: Good morning, Dr. Hanauer, Members of the Committee, Ladies and Gentlemen. My task this morning is to review for you the rationale for treatment of IBS with alosetron, a 5HT3 antagonist. The specific objectives which I hope to cover are the role of serotonin in disease, and I shall give examples of the role of serotonin in irritable bowel syndrome and in carcinoid diarrhea; and, secondly, to review the pharmacodynamic studies that provide the rationale for these 5HT3 antagonists in IBS, specifically the effects on motility, secretion, and sensation.

In a recently published study from Mike Farthing's group in Britain, it was demonstrated that patients with irritable bowel syndrome have post-prandial 5HT levels which are higher than those of healthy controls. Now, the prototype disease that is associated with high pre- and post-prandial levels of 5HT in the circulation is carcinoid diarrhea. This is a severe diarrhea that is associated with a neuroendocrine tumor in which the tumor produces a large amount of serotonin, among other transmitters, and this serotonin spills over into the peripheral plasma and has effect on the way in which the bowel functions.

Indeed, in order to study these patients, we had to develop some novel methodology that allows us to objectively quantify the changes in motor function in the gastrointestinal tract. These novel methodologies are summarized in this slide. Using a gamma camera, and therefore a non-invasive technique, we are able to radio-label a meal and watch and quantitate the rate of emptying from the stomach and from the small intestine of that radio-labeled meal.

At the same time, we provide a different isotope delivered to the distal small intestine in a special methacrylate-coated polymer which dissolves in the distal small intestine, thereby liberating isotope, which then gives us an image of the content moving through the different segments of the colon. And on the next slide you will see that we have illustrated on an actual scan the proportion of isotope in different segments of the colon.

So here's an example of a patient who has carcinoid diarrhea, and we're seeing the isotope located in the different sections of the colon. This isotope is located in the descending colon about one hour after the meal was ingested. Two hours later, most of that isotope has not reached the rectum and is ready for expulsion because of a significant diarrhea.

Now, this is a process that would normally would

take between 25 and 35 hours, and I would emphasize the point that this has occurred in about 3 hours. Therefore, carcinoid diarrhea is associated with rapid emptying of the proximal colon. Quantitative data show that this rate of emptying is about six times that of healthy controls. We also see on this slide that the small bowel transit time is reduced partly as a result of a stimulation of motor function and partly because of the hyper secretion of fluid and electrolytes into the intestine as a result of the serotonin stimulation in the small intestine of these patients.

I would like now to review briefly the pharmacodynamic studies in humans that suggest that the 5HT3 approach would relieve diarrhea and pain, specifically through changes in motor function, fluid and electrolyte absorption, and changes in sensation. Let's first concentrate on the effects of alosetron on motility.

In a study performed by Whorwell and his colleagues in Manchester, United Kingdom, alosetron effect on colonic transit was evaluated in 12 patients with irritable bowel syndrome. This was a randomized double-blind placebo-controlled crossover study in which the dose of 2 milligrams twice a day of alosetron was evaluated. The method used to evaluate transit involved a common and well-validated system, which is the radiopaque marker

transit method. Note here that the alosetron treatment was associated with an increase in the colonic transit time, and that this was predominantly an effect on the left side of the colon.

In studies that we have performed at Mayo Clinic on the effect of alosetron on colonic transit and other parameters in carcinoid diarrhea, we have noted that an increase in the dosage of alosetron, .5 milligrams twice a day to 2 milligrams twice a day, results in a significant three-fold to four-fold reduction in the rate of emptying of the proximal colon. This is associated with a trend in the reduction of 24-hour stool weight in the patients with carcinoid diarrhea.

One of the secondary parameters that we evaluated in that clinical study which consisted of three weeks of treatment with alosetron was to determined the number of tablets of Loperamide that were required as rescue for the control of diarrhea. In patients with carcinoid diarrhea, diarrhea so severe that the patients need to carry an anti-diarrheal with them--and we quantified the number of Loperamide tablets used in this three-week period of time.

Notice in this graph that we have tabulated the cumulative percentage of patients who required equal to or more than five tablets of Loperamide over this three-week period. Notice also that the proportion of patients

requiring rescue with Loperamide decreases with increasing dosage of alosetron in this three-week trial.

What about fluid and electrolyte secretion? In a classical methodology study, Farthing's group has performed triple lumen profusion studies using a 30-centimeter isolated jejunal segment with occluding balloons at each end and the classical marker 14carbon-PEG 4000 as a marker of fluid and electrolyte flux.

Notice that absorption is above the zero line and secretion is below the zero line for both fluid flux and sodium flux. Normally, the small intestine is in a state of absorption for both sodium and for water, as shown by the bar and whisker plot in yellow. Alosetron resulted in an increase in the fluid flux and sodium flux in the absorptive sense, therefore suggesting that alosetron would have an effect in facilitating greater absorption of water and salts in the small intestine in humans.

Finally, let us review briefly some of the studies looking at the effect of alosetron on sensation. In this study by Michel Delvaux and his colleagues, in Toulouse, France, the colon sensation was evaluated by means of a balloon which was placed inside the left part of the colon. Now, in these experiments the volume in order to induce perception of this distension stimulus and the volume to induce a sensation of pain in response to distension is

being recorded and monitored to evaluate the threshold for sensation.

Note that alose tron at these two dosages studied resulted in an increase in the volume to reach perception and an increase in the volume to reach pain threshold, suggesting that the sensitivity of the bowel was being reduced by that treatment. This study, incidentally, was performed in patients with irritable bowel syndrome.

Part of the effect of that change in threshold, that increase in threshold in response to alosetron can be explained by a change in the compliance of the colon. Here, there's an increase in pressure imposed on that segment of colon that is being evaluated. The volume of that segment of colon measured by means of this intracolonic balloon is increased, suggesting that the colon is more compliant; it is able to accommodate a greater volume, for instance, from gas in this case, but presumably also from more solid or liquid components of colonic residue or content.

So, in summary, you've heard that 5HT3 receptors are involved in visceral sensory, secretory, and motor processes in the gastrointestinal tract. Alosetron, which is a selective and potent 5HT3 receptor antagonist, decreases sensitivity to colonic distension, enhances jejunal water and sodium absorption, and slows colonic transit.

I thank you for your attention.

CHAIRMAN HANAUER: Thank you.

The last of the first series of speakers on behalf of Glaxo is Dr. Lin Chang, from UCLA.

DR. CHANG: Good morning. I'm going to speak today about gender differences in gastrointestinal physiology and disease, and particularly focus on irritable bowel syndrome, or IBS.

As you heard earlier from Dr. Wood, irritable bowel syndrome is predominantly seen in females. And there are other chronic pain disorders that are also seen in females more often than in males, and these include chronic constipation, fibromyalgia, chronic fatigue syndrome, interstitial cystitis, migraine headaches, and temporal mandibular joint disorder. These pain disorders share common clinical characteristics and can typically overlap in the same patient, and it has been hypothesized that these chronic pain disorders share a common etiology.

Before I review the gender differences in physiology, I wanted just to review the dimensions of the response to a painful or noxious stimulus. These dimensions include sensory ratings which measure the intensity of a stimulus, affective ratings which measure unpleasantness of a stimulus. There's cognitive, evaluative, physiological and behavioral responses that all contribute to the pain

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Chronology

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Application: Date Range: H

04-Aug-1995 Date Glaxo Wellcome Correspondence

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GR68755 (alosetron hydrochloride) Tablets

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C92-087 with:

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GCP92057 with:

GHP8917 with:

GMH/91/025

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GHP9005 with:

GHP9016 with:

GMH/91/007

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Study Reports

Serial / Supp #

Serial No.: 000 Initial Investigational New Drug Application

C92-006 with: Protocol with Report(s):

GCP/92/019

GMH/91/051

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GPK/91/005

GMH/90/012

GMH/91/002

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Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)

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LAM78906 23-Mar-2000

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S3B201 with: UCP/93/09

S3BB2001 with: GGN/93/010

S3BB2002 with:

GGN/93/011 S3BB2003 with:

GGN/93/012 S3BB2004 with:

GGN/93/013 S3BB2009 with:

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14-Aug-1995 Food and Drug Administration Correspondence

Acknowledgement

IND # Assigned

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Acknowledgement: IND # Assigned

Protocol: S3BA2001

21-Sep-1995 Glaxo Wellcome Telephone Conversation

General Teleconference

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IND 48,487; GR68755 Tablets (alosetron hydrochloride)

General Teleconference: Clinical

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Regulatory Affairs CARDS Chronology

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		ydrochloride)	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Response to FDA Request/Comment Serial No.: 004) X
0004		Response to FDA Request/Comment	Glaxo Wellcome Correspondence	22-Jan-1996
		ydrochloride)	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 003	
0003	Investigator Add	Protocol Amendment: New Investigator	Glaxo Wellcome Correspondence	02-Jan-1996
		ydrochloride) facturing and Controls	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls Serial No.: 001	
0001	CMC	Information Amendment: Chemistry Manufacturing and Controls	Glaxo Wellcome Correspondence	05-Dec-1995
		ydrochloride)	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 002	
0002	Investigator Add	Protocol Amendment: New Investigator	Glaxo Wellcome Correspondence	05-Dec-1995
Control of the state of the sta				
Serial / Sinn #	Document Subtype	Document Type	Communication Type	Date
		tron hydrochloride)	IND 48487; GR68755 Tablets (alosetron hydrochloride)	Application: 1 Date Range: 4
3 09:47:32		CARDS		LAM78906 23-Mar-2000

LAM78906

23-Mar-2000

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4 09:47:32

Date Range: Application: ΑII N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Protocol Amendment: New Investigator Communication Type IND 48,487; GR68755 Tablets (alosetron hydrochloride) Document Type Document Subtype Serial / Supp #

Serial No.: 005

19-Feb-1996 Glaxo Wellcome Correspondence

Protocol Amendment: Change in Protocol

9000

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

Serial No.: 006

28-Feb-1996 Glaxo Wellcome Correspondence

General Correspondence

0007

General Correspondence; Withdrawal of Request for Waivers IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 007

13-Mar-1996 Glaxo Wellcome Correspondence

Protocol Amendment: Change in Protocol

8000

Protocol Amendment: New Investigator

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol

Serial No.: 008

10-Apr-1996 Glaxo Wellcome Correspondence

Protocol Amendment: Change in Protocol

0009

Protocol Amendment: New Investigator

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol

LAM78906 23-Mar-2000

Regulatory Affairs CARDS Chronology

5 09:47:32

Application: IND Date Range: All 48487; GR68755 Tablets (alosetron hydrochloride)

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 009			
19-Apr-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Information Amendment: Chemistry Manufacturing and Controls		0010
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Information Amendment: Chemistry Manufacturing and Controls Serial No.: 010	ıloride) 1g and Controls		
15-May-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0011
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 011	loride)		
18-Jun-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0012
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 012	loride)		
18-Jul-1996	Food and Drug Administration Correspondence	Comment/Information Request	Nonclinical	

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IND 48,487; GR68755 Tablets (alosetron hydrochloride) FDA Comment

CARDS Chronology

6 09:47:32

LAM78906 23-Mar-2000

Application: Date Range: 01-Oct-1996 09-Aug-1996 04-Sep-1996 13-Sep-1996 25-Jul-1996 Date Glaxo Wellcome Correspondence Glaxo Wellcome Correspondence Glaxo Wellcome Correspondence Glaxo Wellcome Correspondence Serial No.: 016 Protocol Amendment: New Investigator Serial No.: 015 Protocol Amendment: New Investigator Protocol Amendment: New Protocol Serial No.: 014 Protocol Amendment: New Investigator Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) IND 48,487; GR68755 Tablets (alosetron hydrochloride) Serial No.: 013 Protocol Amendment: New Investigator Communication Type IND 48,487; GR68755 Tablets (alosetron hydrochloride) IND 48,487; GR68755 Tablets (alosetron hydrochloride) 48487; GR68755 Tablets (alosetron hydrochloride) **Annual Report** Protocol Amendment: New Investigator Protocol Amendment: New Investigator Protocol Amendment: New Protocol Protocol Amendment: New Investigator Protocol Amendment: New Investigator Document Type Foreign Marketing Developments Document Subtype Serial / Supp # 0017 0016 0015 0014 0013

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Regulatory Affairs

Chronology

Date Range: A IN

Application:

23-Mar-2000 LAM78906

48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Document Subtype Serial / Supp #

IND 48,487; Alosetron (GR68755) Tablets

Serial No.: 017 **Annual Report**

13-Nov-1996 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

0018

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 018

22-Nov-1996 Glaxo Wellcome Correspondence

General Correspondence

0019

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

General Correspondence

Serial No.: 019

23-Jan-1997 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

0020

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 020

04-Mar-1997 Glaxo Wellcome Correspondence

General Correspondence

Meeting Request

0021

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Correspondence: Meeting Request - End of Phase II

Serial No.: 021

LAM78906

23-Mar-2000

Regulatory Affairs Chronology CARDS

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Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: <u>~</u>

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Communication Type

8-Mar-1997	Glaxo Wellcome Correspondence
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Document Type

Document Subtype

2

Manufacturing and Controls Information Amendment: Chemistry

Serial / Supp #

0022

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Request for Comment Concerning NDA Stability Program Proposal Information Amendment: Chemistry Manufacturing and Controls

15-Apr-1997 Glaxo Wellcome Correspondence

Protocol Amendment: New Protocol

0023

Protocol Amendment: Change in Protocol

Protocol Amendment: New Investigator

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: Change in Protocol

Protocol Amendment: New Investigator

Serial No.: 023

07-May-1997 Glaxo Wellcome Correspondence

General Correspondence

0024

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

General Correspondence: Background Information for End-of-Phase II Meeting (30 May 1997)

28-May-1997 Glaxo Wellcome Correspondence

Information Amendment: Chemistry

0025

Manufacturing and Controls

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 025

Information Amendment: Chemistry Manufacturing and Controls

Chronology CARDS

9 09:47:32

Application: Date Range: All

23-Mar-2000 LAM78906

48487; GR68755 Tablets (alosetron hydrochloride)

Communication Type

Date

30-May-1997

Glaxo Wellcome Trip Report

End of Phase II Meeting

Document Type

Document Subtype

Serial / Supp #

Type

Type: End of Phase II Meeting IND 48,487; GR68755 Tablets (alosetron hydrochloride)

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

02-Jun-1997

Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Protocol Amendment: New Protocol

0026

Protocol Amendment: New Investigator Protocol Amendment: New Protocol

Serial No.: 026

27-Jun-1997 Food and Drug Administration Correspondence Minutes of Meeting End of Phase II Meeting

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Minutes of Meeting: End of Phase II Meeting

10-Jul-1997 Glaxo Wellcome Correspondence Manufacturing and Controls Information Amendment: Chemistry

0027

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls

11-Jul-1997 Glaxo Wellcome Correspondence

General Correspondence

0029

LAM78906 23-Mar-2000 CARDS Chronology

10 09:47:32

Application: IND Date Range: All 48487; GR68755 Tablets (alosetron hydrochloride)

		Date	
General Correspondence Serial No.: 029	IND 48,487; GR68755 Tablets (alosetron hydrochloride)	Communication Type	
	on hydrochloride)	Document Type	
		Document Subtype	
		Serial / Supp #	

	31-Jul-1997
IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Labeling of Clinical Supplies	31-Jul-1997 Glaxo Wellcome Telephone Conversation
ochloride) upplies	General Teleconference
	CMC

07-Aug-1997		07-Aug-1997
07-Aug-1997 Glaxo Wellcome Correspondence	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence Serial No.: 030	07-Aug-1997 Glaxo Wellcome Correspondence
Protocol Amendment: New Protocol Protocol Amendment: New Investigator	drochloride)	General Correspondence
		CMC
0031		0030

	07-Aug-1997	
IND 48,487; GR68755 Tablets (alosetron hydrochloride)	07-Aug-1997 Glaxo Wellcome Correspondence	
rochloride)	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	
	0031	

Protocol Amendment: New Protocol Protocol Amendment: New Investigator

tron hydrochloride)	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Comment/Information Request	i i
ione Comment/Information Request	28-Aug-1997 Food and Drug Administration Telephone Conversation	28-Aug-1997

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23-Mar-2000 LAM78906 Chronology 11 09:47:32

Application: 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: All

0032		Protocol Amendment: New Investigator	10-Sep-1997 Glaxo Wellcome Correspondence	10-Sep-1997
Serial / Supp #	Document Subtype	Document Type	Communication Type	Date

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator

Serial No.: 032

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IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 033

Protocol Amendment: New Investigator

Protocol: S3BA3001, S3BA3002

				26-Sep-1997	
DID 48 487. CB 68755 Tablets (alacation building block)				26-Sep-1997 Glaxo Wellcome Correspondence	
				Annual Report	
	Outstanding Regulatory Business	CMC	Clinical Study Information	Adverse Event Summary	
				0034	

Annual Report (5-Aug-96 through 4-Aug 97) IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 034

Comment: 5-Aug-96 through 4-Aug-97

	26-Sep-1997	
	26-Sep-1997 Glaxo Wellcome Correspondence	
Protocol Amendment: New Investigator	Protocol Amendment: New Protocol	
	0035	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Serial No.: 035

Protocol with Investigator(s): Protocol: S3BB1011

CARDS

23-Mar-2000 LAM78906 Chronology 09:47:32

Date Range: Application: A I 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Document Subtype Serial / Supp #

S3BB1011 with Aziz L Laurent, M.D.

01-Oct-1997 Glaxo Wellcome Telephone Conversation General Teleconference

CMC

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Response to FDA Request/Comment: CMC

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

03-Oct-1997

Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change

Investigator Add

0036

Protocol Amendment: New Investigator, Investigator Add, Other 1572 Change

Serial No.: 036

Protocol with Investigator(s):

S3BA3001 with:

Jain, M.D., Steven Krumholz, M.D., Oscar Martinez, M.D., Daniel J Pambianco, M.D., Peter M Pardoll, M.D. Hector D Allende, M.D., Caroline T Diamant, M.D., Michael T Draelos, M.D., Robert M Finlaw, M.D., Gregory Fusilier, M.D., Stephen L Green, M.D., Keith P Hussey, M.D., Adesh K

S3BA3002 with:

M.D., Michael Stadiem, M.D., Martin L Throne, M.D., John A Walker, M.D., Gilbert Weisman, DO Linne, M.D., Dennis C. McCluskey, M.D., V C Motaparthy, M.D., Linda P Murray, M.D., Jansi Prabakaran, M.D., Lee R Rocamora, M.D., Charles W Scrowcroft, M.D., David R Silvers Arthur Green, D.O., Daniel E Gremillion, M.D., Paula H Hall, M.D., David A Johnson, M.D., Howard M Kenney, M.D., Robert D Lerner, M.D., Robert L Lindenberg, M.D., James H Raymond L Bell, M.D., Dale Collins, M.D., Michael G DeLissio, M.D., Ervin Eaker, M.D., John K Earl, M.D., Michael F Elmore, M.D., Duane D Fitch, M.D., Martin D Gelfand, M.D.,

09-Oct-1997 Glaxo Wellcome Correspondence Proprietary Name for Alosetron General Correspondence: Request for Review of Lotronex as the IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence Other

0037

14-Oct-1997

Glaxo Wellcome Correspondence

Amendment: Other

Change in Medical Monitor

0038

CARDS

23-Mar-2000 LAM78906 Chronology

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Date Range: Application: ΑII N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Document Subtype Serial / Supp #

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

General Correspondence: Transfer of Obligations to Contract Research Organization

Serial No.: 038

Protocol: S3BA3001, S3BA3002

Comment: Study S3BA3001 conducted by ClinTrials Research Inc.; Study S3BA3002 conducted by ICON Clinical Research; Statistical/pharmacoeconomic analyses for Studies

0039

S3BA3001 and S3BA3002 performed by Quintiles, Inc.; Medical and Safety Monitor: Allen Mangel

23-Oct-1997 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

Serial No.: 039

Protocol with Amendment(s):

S3BB1011 with:

2

03-Nov-1997 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Protocol Amendment: New Protocol Investigator Add

0040

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator Protocol Amendment: New Protocol

Serial No.: 040

Protocol with Amendment(s):

S3BA3003 with:

Investigator: Brandon, Milan

06-Nov-1997 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol Other 1572 Change Investigator Add 0041

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

LAM78906

23-Mar-2000

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09:47:32

Application:

48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

Date

Serial No.: 041 Communication Type Protocol Amendment: New Investigator

Document Type

Document Subtype

Serial / Supp #

Protocol: S3BA2003

Protocol with Amendment(s):

S3BA2002 with:

Protocol with Investigator(s)

S3BA3001 with:

Howard I Siegel, M.D., Lewis Strong, M.D., Robert E Tepper, M.D., Salam Zakko, M.D., Marc J Zuckerman, M.D. A Khairi, M.D., Donald F Kirby, M.D., Terry D. Klein, M.D., Daniel M Kruss, M.D., Susan Lepinski, M.D., Robert S Lipetz, M.D., David G Mangels, M.D., Antoinette Mangione, M.D., James McGill, M.D., William S Mullican, M.D., Zev Munk, M.D., Mark Murphy, M.D., Clinton D Polhamus, M.D., Ronald E Pruitt, M.D., Michael Safdi, M.D., William J Semon, M.D., Gary M Barton, M.D., Robert Burakoff, M.D., Jack A DiPalma, M.D., Robert L Frachtman, M.D., Alan Graff, M.D., Michael R Grossman, M.D., Mario D Kamionkowski, M.D., Rashid

Greg Donald Anderson, M.D., Charles K Bedard, M.D., Scott D Bleser, D.O., Yang K Chen, M.D., Gregory V. Collins, M.D., Raquel Croitoru, M.D., Byron L Cryer, M.D., W. Travis Ellison, M.D., John Gray, M.D., Philip E Jaffe, M.D., David S James, DO, Frank J Konicek, M.D., Mark E Mailliard, M.D., Thomas McDonald, M.D., Trent W Nichols, M.D., Alan Sprague, M.D., Bruce E Stein, M.D., Craig W Wiesenhutter, M.D., Richard A Wright, M.D. Plotner, M.D., Ronald Scott Powell, M.D., Sanjeeva T Reddy, M.D., Michael D Schiff, M.D., Ann L Silverman, M.D., Roger D Soloway, M.D., Marybeth Spanarkel, M.D., Richard S

02-Dec-1997 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Investigator Add

0042

Other 1572 Change

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol with Investigator(s)

Schwarz, M.D., William Wilder, M.D. F Lansdale, M.D., Paul J Lebovitz, M.D., Mark Lott, M.D., Bruce Luxon, M.D., Richard B Lynn, M.D., William Murchison, M.D., Martin Poleski, M.D., Peter M. Ripley, M.D., Ronald Eisdorfer, M.D., Mark Eisner, M.D., Jay L Goldstein, M.D., M Scott Harris, M.D., John M Inadomi, M.D., Ronica Kluge, M.D., David G Kogut, M.D., Richard A Krause, M.D., Thomas Matthew R. Astroff, M.D., D Eric Bolster, M.D., Mark H Bowles, M.D., Howard B Chodash, M.D., Fabio Cominelli, M.D., Vincent A DeLuca, M.D., Sudhir K Dutta, M.D., Robert M.

S3BA3002 with:

S3BA3003 with: William Y Chey, M.D., Alan Cutler, M.D., Ben J Dolin, M.D., Shaban Faruqui, M.D., Richard G Free, M.D., Louis J Gringeri, M.D.

Scott D Bleser, D.O., Milan Brandon, M.D., Eugene J Burbige, M.D., Rokay Kamyar, M.D., Chester W Kessler, M.D., Michael Kurtz, M.D., James Lewis, M.D., Peter L Moses, M.D.,

Thomas J Pulliam, M.D., Patrick Schow, M.D.

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23-Mar-2000 Chronology

Date Range: Application: 48487; GR68755 Tablets (alosetron hydrochloride)

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Date Glaxo Wellcome Correspondence Communication Type Protocol Amendment: Change in Protocol Document Type Document Subtype Serial / Supp #

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

Serial No.: 043

Protocol with Amendment(s):

S3BA3002 with:

15-Jan-1998

Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0044

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator

Protocol with Investigator(s)

S3BA3001 with:

S3BA3002 with: M.D., Michael J Lawson, M.D., Philip B Miner, M.D., Joseph L Nelson, M.D., John Leonard Petrini, M.D., David B Stanton, M.D., Keith G Tolman, M.D., Gregg A Valenzuela, M.D. Lin Chang, M.D., Edward H Cheng, M.D., Douglas A Drossman, M.D., Ronald Fogel, M.D., Oliver D Gilliam, M.D., Peter J Gulden, M.D., Ross A Kommor, M.D., Robert B Lasser,

S3BA3003 with: Jeffrey D Feldstein, M.D., Joseph X Jenkins, M.D., Michael Opipari, M.D., Bennett H Plotnick, M.D., Eamonn M Quigley, M.D., Jean-Pierre Raufman, M.D., W Harley Sobin, M.D.

M.D., James L Conrad, M.D., Charles H DeBusk, M.D., Michael G DeLissio, M.D., Michael F Elmore, M.D., James I Fidelholtz, M.D., Martin D Gelfand, M.D., Daniel E Gremillion, M.D., H Freeman Harris, M.D., William H Holderman, M.D., Robert Holmes, M.D., Dennis C. McCluskey, M.D., Linda P Murray, M.D., Mario Z Rosenberg, M.D., Thomas Rosenfield, M.D., Stephen C Schindler, M.D., Michael Stadiem, M.D., James R Wagner, M.D., John A Walker, M.D., Steven J Wegley, M.D., Gerald D Wolfley, M.D., James D Wolosin, M.D. Richard D. Baerg, M.D., William R. Berry, M.D., Larry R Cain, M.D., Jacques R. Caldwell, M.D., Charles Casale, M.D., Selwyn A Cohen, M.D., Charles L Colip, M.D., Dale Collins,

19-Feb-1998 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0045

Protocol with Investigator(s):

Serial No.: 045

Protocol Amendment: New Investigator

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

S3BA3001 with:

LAM78906

23-Mar-2000

Chronology **CARDS**

Regulatory Affairs

Application: 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: ΑII

Date Communication Type Document Type Document Subtype

Serial / Supp #

09:47:32

S3BA3002 with: David R Cave, M.D., James N Cooper, M.D., M Brian Fennerty, M.D., Charles Melburn Wilcox, M.D

Robert Bruce Cameron, M.D., Ronnie Fass, M.D., Bruce Jones, M.D., Arthur J McCullough, M.D., Frederick Wilson, M.D.

S3BA3003 with:

Charles K Bedard, M.D., Roland William Bennetts, M.D., Charles Casale, M.D., David S James, DO, Thomas Loludice, M.D., William B Smith, M.D.

18-Mar-1998 Food and Drug Administration Correspondence General Correspondence

Status Update

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

General Correspondence: No Objections With Proprietary Name, Lotronex

20-Mar-1998 Glaxo Wellcome Correspondence

Protocol Amendment: Change in Protocol

Clinical

0046

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

Serial No.: 046

Protocol with Amendment(s)

27-Mar-1998

S3BA2002 with:

Glaxo Wellcome Correspondence Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0047

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 047

Protocol: S3BA3001

Protocol with Investigator(s):

S3BA3002 with:

Patricia Raymond, M.D.

S3BA3003 with:

Jim Bauer, M.D., John W Beckman, M.D., Philip C Bird, M.D., William Y Chey, M.D., Michael T Draelos, M.D., John K Earl, M.D., Robert M Finlaw, M.D., Richard Fisher, M.D., Johnson, M.D., John J Jolley, M.D., Lloyd King, M.D., Ross A Kommor, M.D., Mark Lamet, M.D., Robert D Lerner, M.D., David J Miller, M.D., S. David Miller, M.D., Oscar Duane D Fitch, M.D., Walter N Gaman, M.D., Michael W Gorsky, M.D., Russell Graham, M.D., Stephen L Green, M.D., Paula H Hall, M.D., Charles D Hanshaw, M.D., R Bruce

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23-Mar-2000 LAM78906 Chronology 09:47:32

Application:

Date Range:

48487; GR68755 Tablets (alosetron hydrochloride)

Oandasan, M.D., David J Sales, M.D., Douglas Schumacher, M.D., B.N. Shivakumar, M.D., James D Torosis, M.D. Date Communication Type Document Type

> Document Subtype Serial / Supp #

10-Apr-1998 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol

Other 1572 Change Investigator Add

0048

Protocol Amendment: Change in Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 048

Protocol with Amendment(s):

S3BA3002 with:

S3BA3003 with:

Protocol with Investigator(s):

S3BA3001 with:

Gordon V Ohning, M.D.

S3BA3003 with:

Zuckerman, M.D. M.D., Fred Rosenberg, M.D., Ronald Schwarz, M.D., Charles W Scrowcroft, M.D., Bruce E Stein, M.D., William R Stern, M.D., Gilbert Weisman, DO, Barry D Winston, M.D., Marc J Arthur Green, D.O., Bruce Jones, M.D., Steven Krumholz, M.D., David G Mangels, M.D., Frederick H Opper, M.D., Alan Plotner, M.D., Ronald Scott Powell, M.D., Jansi Prabakaran,

06-May-1998 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0049

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator

Serial No.: 049

Protocol: S3BA3001, S3BA3002

Protocol with Investigator(s):

S3BA3003 with:

Charles Franklin Barish, M.D., Thomas D Bianchi, M.D., Jeffrey R Breiter, M.D., Ben J Dolin, M.D., W. Travis Ellison, M.D., Robert L Frachtman, M.D., Gregory Fusilier, M.D., Oliver D Gilliam, M.D., David A Johnson, M.D., Rashid A Khairi, M.D., Sidney F Lauteria, M.D., James McGill, M.D., William S Mullican, M.D., Mark Murphy, M.D., Daniel J Pambianco, M.D., Adisesha B Reddy, M.D., Sanjeeva T Reddy, M.D., Herbert Rubin, M.D., Michael D Schiff, M.D., Patrick Schow, M.D., Salam Zakko, M.D.

11-May-1998 Glaxo Wellcome Correspondence

10-Day ADR Report

Initial

0051

23-Mar-2000 LAM78906 Chronology **CARDS**

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Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: All

Date Communication Type IND 48,487; GR68755 Tablets (alosetron hydrochloride) Document Type Document Subtype Serial / Supp #

10-Day ADR Report: Initial

Serial No.: 051

Protocol: S3BA3003 ADR: A0064427A

12-May-1998 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol Clinical 0050

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

Serial No.: 050

Protocol with Amendment(s):

S3BA3002 with:

04-Jun-1998

Glaxo Wellcome Correspondence

10-Day ADR Report

Follow-up

0052

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

10-Day ADR Report: Follow-up

Serial No.: 052

Protocol: S3BA3003 ADR: A0064427A

10-Jun-1998 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol

0053

Protocol with Amendment(s):

Serial No.: 053

S3BA3001 with:

01, 02, 03

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•	18-Jun-1998	
	Glaxo Wellcome Correspondence	
	Protocol Amendment: New Investigator	
Other 1572 Change	Investigator Add	
	0055	

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Application: A IN 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

23-Mar-2000 LAM78906

Date Communication Type Document Type Document Subtype Serial / Supp #

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 055

Protocol: S3BA3001

Protocol with Investigator(s):

S3BA3003 with:

Krause, M.D., Daniel M Kruss, M.D., Michael S Levine, M.D., Robert L Lindenberg, M.D., James H Linne, M.D., Oscar Martinez, M.D., Thomas McDonald, M.D., Michael Opipari, M.D., Stephen D Pershing, M.D., Bennett H Plotnick, M.D., Ronald E Pruitt, M.D., Ann L Silverman, M.D., Eugene Spiotta, M.D., Lewis Strong, M.D., Robert E Tepper, M.D., M. Scott Fabio Cominelli, M.D., Raquel Croitoru, M.D., Vincent A DeLuca, M.D., Michael R Grossman, M.D., M Scott Harris, M.D., David G Kogut, M.D., George Koval, M.D., Richard A Touger, M.D., Craig W Wiesenhutter, M.D.

S3BA3003 with: Protocol with Amendment(s): 24-Jun-1998 18-Jun-1998 Glaxo Wellcome Correspondence Glaxo Wellcome Correspondence Serial No.: 054 Protocol Amendment: Change in Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Clinical 0056 0054

Protocol Amendment: New Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Investigator Add

Protocol with Investigator(s):

Serial No.: 056

Protocol Amendment: New Investigator

S3B30004 with:

Douglas A Drossman, M.D.

			l
		13-Jul-1998	
		-Jul-1998 Glaxo Wellcome Correspondence	
	Protocol Amendment: New Investigator	Protocol Amendment: Change in Protocol	
Other 1577 Change	Investigator Add	Clinical	
		0057	

Chronology CARDS

Application: AI N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

23-Mar-2000 LAM78906

Date Communication Type Document Type

Document Subtype

Serial / Supp #

20 09:47:32

Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 057

Protocol with Amendment(s):

S3BA3002 with:

Protocol with Investigator(s):

S3BA3003 with:

Sudhir K Dutta, M.D., Paul J Lebovitz, M.D., Peter L Moses, M.D., Gordon V Ohning, M.D., Clinton D Polhamus, M.D., Richard A Wright, M.D.

16-Jul-1998 Glaxo Wellcome Correspondence 10-Day ADR Report: Follow-up IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Follow-up

0058

Serial No.: 058

Protocol: S3BA3003 ADR: A0064427A

17-Jul-1998 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Protocol

0059

Protocol Amendment: New Investigator Serial No.: 059

Protocol with Investigator(s):

S3B20013 with: William Y Chey, M.D.

22-Jul-1998 Glaxo Wellcome Correspondence 10-Day ADR Report Initial 0060

IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial

Serial No.: 060

CARDS

09:47:32 21

Application: 23-Mar-2000 N 48487; GR68755 Tablets (alosetron hydrochloride) Chronology

Date Range: ΑII

LAM78906

ADR: A0067942A Date Communication Type Document Type Document Subtype Serial / Supp #

Protocol: S3BA3003

23-Jul-1998 Glaxo Wellcome Correspondence Manufacturing and Controls Information Amendment: Chemistry

CMC 0061

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 061 Information Amendment: Chemistry Manufacturing and Controls

27-Jul-1998

Glaxo Wellcome Correspondence

Protocol Amendment: New Protocol

0063

Protocol Amendment: New Investigator

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator Protocol Amendment: New Protocol

Serial No.: 063

Protocol with Investigator(s):

S3BA1006 with:

William Y Chey, M.D.

27-Jul-1998 Glaxo Wellcome Correspondence

Protocol Amendment: New Protocol

0062

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol

Serial No.: 062

Protocol with Amendment(s):

S3BA1002 with:

. 01,02

Protocol with Investigator(s):

S3BA1002 with:

Chronology CARDS

22 09:47:32

Application: Date Range: ΑII N 48487; GR68755 Tablets (alosetron hydrochloride)

23-Mar-2000 LAM78906

Samuel Serfaty, M.D. Date Communication Type Document Type Document Subtype Serial / Supp #

Protocol Amendment: Change in Protocol

Protocol Amendment: New Investigator

04-Aug-1998

Glaxo Wellcome Correspondence

Other 1572 Change Investigator Add

0064

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol

Serial No.: 064

Protocol: S3BA3002

Protocol with Amendment(s):

S3BA1002 with:

Protocol with Investigator(s):

S3BA3001 with:

David George Scholz, M.D.

S3BA3003 with:

Thomas Anthony Carr, M.D., Robert Murphy, M.D.

17-Aug-1998 Glaxo Wellcome Telephone Conversation General Teleconference

General Teleconference IND 48,487; GR68755 Tablets (alosetron hydrochloride)

31-Aug-1998 Food and Drug Administration FAX/E-mail

General Memorandum

Meeting Request Meeting Agenda or Details

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

General Memorandum: Meeting Request

02-Sep-1998 Glaxo Wellcome Correspondence

Annual Report

Clinical Study Information Adverse Event Summary

0065

CARDS Chronology

23 09:47:32

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: All

LAM78906 23-Mar-2000

Date Communication Type Document Type Document Subtype Serial / Supp #

Investigational Plan

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Annual Report Serial No.: 065

Protocol: S3B30004, S3BA2001, S3BA2002, S3BA2003, S3BA3001, S3BA3002, S3BA3003, S3BB1003, S3BB1011, S3BB2011

Comment: Period Covering: 05 August 1997 through 04 August 1998

10-Sep-1998

Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change

Investigator Add

0066

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator

Serial No.: 066

Protocol: S3B20013, S3BA3002

Protocol with Investigator(s):

S3B30004 with:

Michael D Crowell, M.D.

S3BA3001 with:

Thomas J Chiambretti, D.O.

S3BA3003 with: Lin Chang, M.D., Thomas J Chiambretti, D.O., Douglas A Drossman, M.D., Richard White, M.D.

14-Sep-1998 Glaxo Wellcome Correspondence

Protocol Amendment: Change in Protocol

Clinical

0067

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

Serial No.: 067

Protocol with Amendment(s):

S3BA2002 with:

. 'S3BA3001 with:

04

Chronology CARDS

24 09:47:32

Application: Date Range: All ND 48487; GR68755 Tablets (alosetron hydrochloride)

23-Mar-2000 LAM78906

15-Sep-1998 Date Glaxo Wellcome Correspondence Communication Type Document Type 10-Day ADR Report Follow-up Document Subtype Serial / Supp # 8900

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

10-Day ADR Report: Follow-up

Serial No.: 068

ADR: A0067942A Protocol: S3BA3003

15-Sep-1998 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Initial 0069

10-Day ADR Report: Initial

Serial No.: 069

ADR: A0070295A Protocol: S3BA3003

05-Oct-1998		25-Sep-1998
05-Oct-1998 Glaxo Wellcome Correspondence	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence	25-Sep-1998 Glaxo Wellcome Correspondence
10-Day ADR Report	drochloride)	General Correspondence
Follow-up		Clinical
0070		

Protocol: S3BA3003 ADR: A0070295A

Serial No.: 070

10-Day ADR Report: Follow-up

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

16-Oct-1998 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Investigator Add Other 1572 Change 0071

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Application: 23-Mar-2000 AII ND 48487; GR68755 Tablets (alosetron hydrochloride) Chronology

Date Range: Date Communication Type

LAM78906

Serial No.: 071

Protocol Amendment: New Investigator

Document Type

Document Subtype

Serial / Supp #

Protocol: S3BA3002

Protocol with Investigator(s):

Philip O Katz, M.D. S3B20012 with:

S3B30004 with:

William Y Chey, M.D., Arthur Green, D.O.

S3BA3003 with:

Patricia Raymond, M.D.

26-Oct-1998 Glaxo Wellcome Correspondence Minutes of Meeting FDA Conference

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Minutes of Meeting: October 6, 1998 to Discuss the Quality of Life Program for Alosetron

26-Oct-1998 Glaxo Wellcome Correspondence

10-Day ADR Report

Initial

0072

10-Day ADR Report: Initial

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 072

Protocol: S3BB3002 ADR: B0060594A

05-Nov-1998 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator Protocol Amendment: New Protocol

Investigator Add

0073

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Serial No.: 073

Protocol with Investigator(s):

CARDS

25 09:47:32

CARDS

26 09:47:32

LAM78906 23-Mar-2000 Chronology

Date Range: Application: ΑII N 48487; GR68755 Tablets (alosetron hydrochloride)

Benoit Girard, M.D. Date Communication Type Document Type Document Subtype Serial / Supp #

06-Nov-1998 Glaxo Wellcome Correspondence 10-Day ADR Report

Follow-up

0075

10-Day ADR Report: Follow-up IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 075

Protocol: S3BB3002 ADR: B0060594A

09-Nov-1998 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Protocol Amendment: New Protocol Investigator Add 0074

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator Protocol Amendment: New Protocol

Serial No.: 074

Protocol with Investigator(s):

S3B30006 with:

Charles Franklin Barish, M.D., John W Beckman, M.D., D Eric Bolster, M.D., William Y Chey, M.D., John K Earl, M.D., Robert M Finlaw, M.D., Robert Holmes, M.D., Robert D Lerner, M.D., Donato Ricci, M.D., Stephen C Schindler, M.D.

10-Nov-1998 Glaxo Wellcome Correspondence Manufacturing and Controls Information Amendment: Chemistry CMC 0076

Information Amendment: Chemistry Manufacturing and Controls, CMC IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 076

20-Nov-1998 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol Clinical 0077

Protocol Amendment: Change in Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride)

CARDS

23-Mar-2000 LAM78906 Chronology 09:47:32

Application: A Z 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

Date

Communication Type

Document Type

Document Subtype

Serial / Supp #

Serial No.: 07

Protocol with Amendment(s):

S3BA3003 with:

20

23-Nov-1998 Food and Drug Administration Telephone Conversation General Teleconference

General Teleconference: Other IND 48,487; GR68755 Tablets (alosetron hydrochloride)

FDA request for submission of DDMAC Meeting (6 October 1998) Summary to IND

General Discussion Regarding NDA Plans

Commitment: Submit request for pre-NDA meeting

Commitment Responsibility: Mark Baumgartner Commitment Due Date: 15-Jan-1999

24-Nov-1998 Glaxo Wellcome Correspondence 10-Day ADR Report

Initial

0078

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

10-Day ADR Report: Initial

Serial No.: 078

ADR: A0070339A Protocol: S3BA3001

01-Dec-1998 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol Protocol Amendment: New Protocol Clinical 0079

Protocol Amendment: New Protocol

Protocol Amendment: Change in Protocol

Serial No.: 079 Protocol Amendment: New Investigator

Protocol with Amendment(s):

Chronology **CARDS** 28 09:47:32

Application: N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: All

LAM78906

23-Mar-2000

Protocol with Investigator(s):

S3BA1004 with:

Date

Communication Type

Document Type

Document Subtype

Serial / Supp #

S3BA1004 with:

Ronald Goldwater, M.D.

04-Dec-1998 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Minutes of Meeting FDA Conference 0080

Minutes of Meeting: FDA Conference

Serial No.: 080

Comment: Quality of Life Program

07-Dec-1998 Glaxo Wellcome Correspondence Protocol Amendment: New Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol

0081

Protocol with Report(s): S3B20015 with:

Serial No.: 081

RM1998/00464/00

11-Dec-1998 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Follow-up 0082

Serial No.: 082 10-Day ADR Report: Follow-up

Protocol: S3BA3001

ADR: A0070339A

15-Dec-1998 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Other 1572 Change Investigator Add

0083

Protocol Amendment: New Investigator

CARDS

Chronology

Application: 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

Date

Communication Type

Document Type

Document Subtype

Serial / Supp #

29 09:47:32

Serial No.: 083

23-Mar-2000 LAM78906

Protocol: S3B20012, S3BA2002, S3BA3001, S3BA3002, S3BA3003

Protocol with Investigator(s):

S3B30004 with:

Michael T Draelos, M.D

S3B30006 with:

Richard D. Baerg, M.D., Jim Bauer, M.D., William R. Berry, M.D., Jeffrey R Breiter, M.D., Michael F Elmore, M.D., Richard Fisher, M.D., Duane D Fitch, M.D., Larry I Gilderman, M.D., Stephen L Green, M.D., Arnold O Hopland, M.D., Bruce Jones, M.D., Richard A Krause, M.D., Steven Krumholz, M.D., Jake C Lennard, M.D., Frederick H Opper, M.D., Clinton D Polhamus, M.D., Sidney Rosenblatt, M.D., Herbert Rubin, M.D., David J Sales, M.D., Eugene Spiotta, M.D., Michael Stadiem, M.D., Kevin L Tack, M.D., Troy Alan Tyner, M.D., Barry D Winston, M.D., James D Wolosin, M.D.

21-Dec-1998 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence Protocol 0084

Protocol: S3BA3003

Serial No.: 084

General Correspondence: Protocol

21-Dec-1998 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol

Clinical

0085

Protocol Amendment: Change in Protocol, Clinical IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 085

Protocol with Amendment(s):

S3BA1006 with:

2

	08-Jan-1999	
	Glaxo Wellcome Correspondence	
Manufacturing and Controls	Information Amendment: Chemistry	
	CMC	
	0086	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 086 Information Amendment: Chemistry Manufacturing and Controls, CMC

Protocol: S3B20015

Regulatory Affairs CARDS

Chronology 30 09:47:32

Application: IND Date Range: All 48487; GR68755 Tablets (alosetron hydrochloride)

LAM78906 23-Mar-2000

Date Communication Type	Document Type	Document Subtype Serial / S	Supp #
08-Jan-1999 Glaxo Wellcome Telephone Conversation	General Teleconference	Request Status Update	
R68755 Tablets (alosetron hydrochlor	ride)		
ু ল 1 ≦	hydrochlo	hydrochlo	General Teleconference Request

General Teleconference: Request Status Update

	13-Jan-1999
IND 48,487; GR68755 Tablets (alosetron hydrochloride) Comment/Information Request: CMC	13-Jan-1999 Food and Drug Administration Correspondence
loride)	Comment/Information Request
	CMC

13-Jan-1999	
Food and Drug Administration Correspondence	
Minutes of Meeting	
FDA Conference	

18-Jan-1999			
18-Jan-1999 Glaxo Wellcome Correspondence	Minutes of Meeting: Discuss Health-Related Quality of Life Endpoints in Phase 3 Studies	IND 48,487; GR68755 Tablets (alosetron hydrochloride)	•
General Correspondence	ality of Life Endpoints in Phase 3 Studies	chloride)	
Meeting Request			
0087			

18-Jan-1999	18-Jan-1999 Glaxo Wellcome Correspondence	General Correspondence	Meeting Request
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: Request for Pre-NDA Meeting Serial No.: 087	drochloride) DA Meeting	
21-Jan-1999	21-Jan-1999 Glaxo Wellcome Correspondence	Minutes of Meeting	Pre-NDA Meeting
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Minutes of Meeting: Request for Clarification	drochloride)	

22-Jan-1999 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Investigator Add

8800

Chronology **CARDS**

31 09:47:32

Date Range: Application: A IZ 48487; GR68755 Tablets (alosetron hydrochloride)

Date

Communication Type

23-Mar-2000 LAM78906

Document Type

Other 1572 Change

Document Subtype

Serial / Supp #

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 088

Protocol: S3BA3003

Protocol with Investigator(s):

S3B30006 with:

M.D., Earl Glen Robbins, M.D., Michael Safdi, M.D., Ronald Schwarz, M.D., John Q Stauffer, M.D., Bruce E Stein, M.D., Robert E Tepper, M.D., James R Wagner, M.D., Gilbert Oscar Martinez, M.D., H. Charles Miller, M.D., Philip B Miner, M.D., William S Mullican, M.D., James Novick, M.D., Alan Plotner, M.D., Bennett H Plotnick, M.D., Joseph Reddy, Weisman, DO, Gerald D Wolfley, M.D., William C Wu, M.D. Kallianos, M.D., George Koval, M.D., Michael Kurtz, M.D., Edwin Larkai, M.D., Desmond Leddin, M.D., Michael S Levine, M.D., Thomas Liebermann, M.D., Thomas Loludice, DO, M.D., Komaranahalli P Ganeshappa, M.D., Arthur Green, D.O., Michael R Grossman, M.D., William H Holderman, M.D., David S James, DO, R Bruce Johnson, M.D., John Andrew DeLissio, M.D., Michael T Draelos, M.D., Margaret A. Drehobl, M.D., W. Travis Ellison, M.D., John E Ervin, M.D., James I Fidelholtz, M.D., David L Fried, M.D., Syam P Gaddam, Hector D Allende, M.D., Scott D Bleser, D.O., Lawrence F Blob, M.D., Jacques R. Caldwell, M.D., Dale Collins, M.D., James L Conrad, M.D., Douglas D Dalke, M.D., Michael G

S3BA3002 with:

Patrick Schow, M.D.

0090	Clinical	Protocol Amendment: Change in Protocol	26-Jan-1999 Glaxo Wellcome Correspondence	26-Jan-1999
		ydrochloride) A Meeting Minutes	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: Response to FDA Meeting Minutes Serial No.: 089	
0089	Other	General Correspondence	22-Jan-1999 Glaxo Wellcome Correspondence	22-Jan-1999

Protocol with Amendment(s):

Serial No.: 090

Protocol Amendment: Change in Protocol

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

S3B30006 with:

01, 02, 03

27-Jan-1999 Food and Drug Administration FAX/E-mail

General Memorandum

Meeting Agenda or Details

LAM78906 23-Mar-2000 Chronology CARDS 32 09:47:32

Date Range: Application: A I 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Document Subtype

Serial / Supp #

General Memorandum IND 48,487; GR68755 Tablets (alosetron hydrochloride)

29-Jan-1999 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol

Clinical

0091

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol

Serial No.: 091

Protocol with Amendment(s):

S3BA3001 with:

Protocol with Report(s):

S3BA3001 with:

RM1997/000534/05

29-Jan-1999 Glaxo Wellcome Correspondence Serial No.: 092 10-Day ADR Report: Follow-up IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Follow-up

0092

ADR: A0067942A Protocol: S3BA3003

12-Feb-1999 Glaxo Wellcome Correspondence Amendment: Other Protocol Amendment: Change in Protocol Research Organization Clinical Transfer of Obligations to Contract 0093

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

Serial No.: 093 Amendment: Other, Transfer of Obligations to Contract Research Organization

Protocol with Amendment(s):

CARDS

23-Mar-2000 LAM78906 Chronology

Date Range: Application: ΑII N

48487; GR68755 Tablets (alosetron hydrochloride)

S3B20015 with: Date Communication Type Document Type

Comment: ICON Clinical Research, Inc. 115 East Park Drive, Suite 200, Brentwood, TN 37027

12-Feb-1999 Glaxo Wellcome Correspondence

10-Day ADR Report

Initial

Document Subtype

Serial / Supp #

0094

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

10-Day ADR Report: Initial

Serial No.: 094

ADR: B0062540A Protocol: S3BB3001

17-Feb-1999 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol

Other 1572 Change Investigator Add Clinical

0095

Protocol Amendment: Change in Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 095 Protocol Amendment: New Investigator, Investigator Add

Protocol: S3BA3003

S3B30006 with: Protocol with Amendment(s):

Protocol with Investigator(s):

S3B30006 with:

M.D., Robert L Lindenberg, M.D., David G Mangels, M.D., Joseph L Nelson, M.D., Oscar Oandasan, M.D., Pierre Pare, M.D., Deepen Patel, M.D., J Mark Provenza, M.D., Thomas J Charles K Bedard, M.D., Michael T Bennett, M.D., Georges Choueri, M.D., Fabio Cominelli, M.D., Paula A Hall, M.D., Rashid A Khairi, M.D., James C Kisicki, M.D., Ross A Kommor, Pulliam, M.D., Allen Rubin, M.D., Per Sangfelt, M.D., Charles J Sigmund, M.D., Tom Storskrubb, M.D., Paul F Whitsitt, M.D., Marc J Zuckerman, M.D.

S3BA3001 with:

John K DiBaise, M.D.

18-Feb-1999 Glaxo Wellcome Correspondence

Protocol Amendment: Change in Protocol

Clinical

33 09:47:32

Protocol Amendment: Change in Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride)

0096

Regulatory Affairs CARDS

Chronology

34 09:47:32

23-Mar-2000 LAM78906

Date Range: Application: Date AI N Communication Type Serial No.: 096 48487; GR68755 Tablets (alosetron hydrochloride) Document Type Document Subtype Serial / Supp #

Protocol with Amendment(s):

ន S3B20015 with:

26-Feb-1999 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol Clinical 0097

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

Serial No.: 097

Protocol with Amendment(s):

S3BA3003 with:

03-Mar-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change Investigator Add 0098

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator

Serial No.: 098

Protocol: S3B20012, S3B30004

Protocol with Investigator(s):

S3B30006 with:

William Bennetts, M.D., Einar Bjornsson, M.D., Sudhir K Dutta, M.D., Marie Fellke, M.D., Oliver D Gilliam, M.D., M Scott Harris, M.D., Marc S Kaufman, M.D., S Jon Mason, M.D., Gunnar Midhagen, M.D., Lars Sidenvall, M.D., David R Silvers, M.D., Amit Kumar Srivastava, M.D., Richard White, M.D., Ellis E Williams, M.D.

12-Mar-1999 Glaxo Wellcome Correspondence General Correspondence: Pre-NDA Meeting Background Package IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence Meeting Agenda or Details

0099

Serial No.: 099

15-Mar-1999 Glaxo Wellcome Correspondence

Information Amendment: Clinical

Safety

0100

CARDS

35 09:47:32

23-Mar-2000 LAM78906 Chronology

Date Range: Application: AII D 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Study Reports Document Subtype Serial / Supp #

Information Amendment: Clinical IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 100

Protocol with Report(s):

RM1998/00429/00 S3BA3001 with:

S3BA3002 with:

RM1998/00430/00

16-Mar-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Investigator Add

0101

Protocol: S3BA1001, S3BA2002, S3BA3003 Serial No.: 101

Protocol with Investigator(s):

S3B20015 with:

Scott D Bleser, D.O., Troy Alan Tyner, M.D.

S3B30006 with:

Ian Barrison, M.D., Paul J Lebovitz, M.D., Mark L Lloyd, M.D., Seymour Mishkin, M.D., Henry Nyhlin, M.D., Marybeth Spanarkel, M.D., Nigel Stace, M.D., John A Walker, M.D.

General Memorandum

Safety

24-Mar-1999 Glaxo Wellcome FAX/E-mail

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

General Memorandum: Safety

Protocol: S3BB3001

ADR: B0065097A

25-Mar-1999 Glaxo Wellcome FAX/E-mail

General Memorandum

Safety

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

General Memorandum: Safety

CARDS

23-Mar-2000 LAM78906 Chronology 36 09:47:32

Application: Date Range: All N 48487; GR68755 Tablets (alosetron hydrochloride)

ADR: B0065097A Protocol: S3BB300 Date Communication Type Document Type Document Subtype Serial / Supp #

26-Mar-1999 Glaxo Wellcome Telephone Conversation

General Teleconference Meeting Agenda or Details

General Teleconference: Meeting Agenda or Details IND 48,487; GR68755 Tablets (alosetron hydrochloride)

29-Mar-1999

Glaxo Wellcome Correspondence

10-Day ADR Report

Initial

0102

10-Day ADR Report: Initial IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 102

Protocol: S3BB3001 ADR: B0065097A

05-Apr-1999 Glaxo Wellcome Correspondence 10-Day ADR Report Initial

0103

IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial

Serial No.: 103

Protocol: S3BB3002

ADR: B0065267A

13-Apr-1999 Glaxo Wellcome Telephone Conversation General Teleconference Meeting Agenda or Details

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

General Teleconference: Meeting Agenda or Details

15-Apr-1999 Glaxo Wellcome Trip Report

Type

Pre-NDA Meeting

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Chronology CARDS

Application: N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: ΑII 23-Mar-2000 LAM78906

Type: Pre-NDA Meeting

Communication Type

Document Type

Document Subtype

Serial / Supp #

09:47:32

Date

16-Apr-1999 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0105

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 105

Protocol: S3B30004, S3BA3003

S3B20015 with: Protocol with Investigator(s):

M.D., Richard A Krause, M.D., Daniel M Kruss, M.D., Edwin Larkai, M.D., Oscar Oandasan, M.D., Vinod Rustgi, M.D., Howard I. Schwartz, M.D., Eugene Spiotta, M.D., Gerald D Charles Franklin Barish, M.D., John W Beckman, M.D., Johnthan M. Bern, M.D., Milan Brandon, M.D., John K Earl, M.D., Duane D Fitch, M.D., David S James, DO, Bruce Jones, Wolfley, M.D., James D Wolosin, M.D.

S3B30006 with:

Sydney Bass, M.D., Frederick M. Braunstein, M.D., Thomas Anthony Carr, M.D., Lin Chang, M.D., Loganathon Govender, M.D., H Freeman Harris, M.D., Antony Barnabas Hawthorne, Thomas Andrew Sylwestowicz, M.D., David Troughton, M.D., Ian Wallace, M.D., D. E. Ward, M.D., Mike Watson, M.D., Craig W Wiesenhutter, M.D. M.D., Simon K Holgate, M.D., John M Inadomi, M.D., Bernard King, M.D., Alan Lane, M.D., Anna Maclean, M.D., Gordon V Ohning, M.D., Vinod Rustgi, M.D., Bruce E Stein, M.D.,

16-Apr-1999 Glaxo Wellcome Correspondence

10-Day ADR Report

Follow-up

0104

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

10-Day ADR Report: Follow-up

Serial No.: 104

ADR: B0065267A Protocol: S3BB3002

26-Apr-1999 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0107

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator

Serial No.: 0107

CARDS

23-Mar-2000 LAM78906 Chronology

Date Range: Application: AII N 48487; GR68755 Tablets (alosetron hydrochloride)

Protocol: S3BA3003, S3BA3004 Date Communication Type

Document Type

Document Subtype

Serial / Supp #

38 09:47:32

Protocol with Investigator(s):

S3B20015 with:

Strimling, M.D., Robert E Tepper, M.D. M.D., Philip B Miner, M.D., Daniel J Pambianco, M.D., Vinod Rustgi, M.D., Shahriar S Safavi, M.D., Herbert Schneider, M.D., Ronald Schwarz, M.D., Bruce E Stein, M.D., Michael Ian Berkowitz, M.D., Luis Bujanda, M.D., William Y Chey, M.D., Michael T Draelos, M.D., Jack H Hall, M.D., Steven Krumholz, M.D., Thomas Liebermann, M.D., Oscar Martinez,

S3B30006 with:

Gilbert O Barbezat, M.D., Karna Dev Bardhan, M.D., Adrian Darrah, M.D., Montserrat Forne, M.D., Robert K Hippert, D.O., P B Irwin, M.D., David A Johnson, M.D., Michael P Jones, M.D., Chris Kyle, M.B., B.Ch., Alan Robert McFarland, M.D., H P McGoldbrick, M.D.

S3BA3002 with:

David S Hodges, M.D.

26-Apr-1999 Glaxo Wellcome Correspondence Serial No.: 0106 10-Day ADR Report: Follow-up IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Follow-up 0106

Protocol: S3BB3001 ADR: B0065097A

26-Apr-1999 Glaxo Wellcome FAX/E-mail Response to FDA Request/Comment Clinical

Protocol: S3BA2001

Response to FDA Request/Comment: Clinical

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

27-Apr-1999 Food and Drug Administration Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Comment/Information Request Comment/Information Request

Comment: Clarification of Minutes from Oct 6, 1998 meeting

. 12-May-1999	Food and Drug Admir	Minutes of Meeting	Pre-NDA Meeting
		C	•

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

23-Mar-2000 LAM78906 Chronology CARDS

39 09:47:32

Application: Date Range: A D 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Document Subtype Serial / Supp #

Minutes of Meeting: Pre-NDA Meeting

17-May-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0108

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0108

Protocol: S3BA3003

Protocol with Investigator(s)

S3B20015 with:

S3B30006 with: M.D., William H Holderman, M.D., George Koval, M.D., Mark Lamet, M.D., Robert D Lerner, M.D., Dennis C. McCluskey, M.D., Arturo Perez Mota, M.D., William S Mullican, M.D., Charles K Bedard, M.D., Charles Noah Berstein, M.D., FRCP(C), Harold Bloch, M.D., Jacques R. Caldwell, M.D., Fernando Carballo, M.D., Robert M Finlaw, M.D., Stephen L Green, Igor Prokopiw, M.D., Luis Rodrigo, M.D., John Philip Wright, M.D.

Janusz Jankowski, M.D., Chester W Kessler, M.D., Steve Lillis, M.D.

20-May-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment Other Clinical

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Response to FDA Request/Comment: Draft of the Benefit and Risks and ISE

Serial No.:

25-May-1999 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0109

Protocol Amendment: New Investigator

Protocol Amendment: Change in Protocol

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0109

Protocol: S3B30004, S3B30006, S3BA3003

CARDS

23-Mar-2000 LAM78906 Chronology 40 09:47:32

Application: IND Date Range: All 48487; GR68755 Tablets (alosetron hydrochloride)

S3B20013 with:

Protocol with Amendment(s):

Date Communication Type

Document Type

Document Subtype

Serial / Supp #

Protocol with Investigator(s): S3B20015 with:

Thomas Loludice, DO, James R Wagner, M.D.

Protocol with Report(s):

S3B20013 with:

RM1998/00185/01

25-May-1999 Glaxo Wellcome Correspondence 10-Day ADR Report

0110

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

10-Day ADR Report: Initial

Serial No.: 0110

Protocol: S3B30006 ADR: B0066851A

27-May-1999 Glaxo Wellcome Correspondence General Correspondence CMC BA/BE Clinical Nonclinical 0111

General Correspondence: FDA Response Requested IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Plans to Address FDA Comments and Requests FDA Pre-NDA Meeting Minutes: Request for Clarification

Serial No.: 0111

Protocol: S3BA2001, S3BB1004

02-Jun-1999 Glaxo Wellcome Telephone Conversation General Teleconference CMC Clinical Meeting Agenda or Details

Nonclinical

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

CARDS

23-Mar-2000 LAM78906 48487; GR68755 Tablets (alosetron hydrochloride) Chronology 41 09:47:32

Date Range: Application: Comment: Response to FDA request for information 15-Jun-1999 09-Jun-1999 14-Jun-1999 03-Jun-1999 Date AI I Glaxo Wellcome Telephone Conversation Glaxo Wellcome Correspondence Glaxo Wellcome Telephone Conversation General Teleconference: Clinical, CMC, Meeting Agenda or Details, Nonclinical Food and Drug Administration Telephone IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Teleconference: Clinical, CMC, Nonclinical, Request Status Update IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Status Update IND 48,487; GR68755 Tablets (alosetron hydrochloride) Conversation Communication Type General Teleconference: Clinical, CMC, Meeting Agenda or Details, Nonclinical Protocol Amendment: New Investigator General Teleconference General Teleconference General Teleconference Document Type CMC Clinical CMC Other 1572 Change Investigator Add Status Update Nonclinical Meeting Agenda or Details Request Status Update Nonclinical Clinical Document Subtype Serial / Supp # 0112

Serial No.: 0112

Protocol Amendment: New Investigator

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Chronology CARDS

42 09:47:32

Application: 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: AII D 23-Mar-2000 LAM78906

Date Communication Type Document Type Document Subtype Serial / Supp #

Protocol: S3B30006, S3BA3003

Protocol with Investigator(s):

S3B20015 with:

Wetterhus, M.D., Richard White, M.D. Dale Collins, M.D., Enrique Dominguez, M.D., W. Travis Ellison, M.D., Per G Farup, M.D., Ulf Fjosne, M.D., Ole Hoie, M.D., E Walter Hood, M.D., Rokay Kamyar, M.D., Paul J Lebovitz, M.D., Michael S Levine, M.D., Jacob Louw, Professor, David A Peura, M.D., Michael Safdi, M.D., Asbjom Stallemo, M.D., Roald Torp, M.D., John A Walker, M.D., Sigurd

17-Jun-1999 Food and Drug Administration Correspondence Comment/Information Request CMC

Clinical

Nonclinical

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Comment/Information Request: Clinical, CMC, Nonclinical

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

18-Jun-1999

Glaxo Wellcome Telephone Conversation,

General Teleconference

Other Clinical

General Teleconference: Clinical, Other

Comment: Call to clarify the FDA fax of 17 June 1999; response to GWletter of 27 May 1999

24-Jun-1999

Glaxo Wellcome Correspondence

Other 1572 Change Investigator Add

0113

Protocol Amendment: New Investigator

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0113

Protocol with Investigator(s)

S3B20015 with:

Roland William Bennetts, M.D., Michel Boivin, M.D., Michael Kurtz, M.D., Charles W Scowcroft, M.D., Arne W Wilskow, M.D.

S3B30006 with:

Gary E Poleynard, M.D

CARDS Chronology

43 09:47:32

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: All

LAM78906 23-Mar-2000

24-Jun-1999 Date Glaxo Wellcome Telephone Conversation Communication Type Response to FDA Request/Comment Document Type Clinical Document Subtype Serial / Supp #

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Response to FDA Request/Comment: Clinical

07-Jul-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Protocol Amendment: New Protocol Investigator Add

0114

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Serial No.: 0114

Protocol with Investigator(s):

S3B10906 with:

Michael Camilleri, M.D. Protocol with Report(s):

S3B10906 with:

NN1999/00052/00

	12-Jul-1999
IND 48,487; GR68755 Tablets (alosetron hydrochloride General Correspondence: Clinical, Meeting Request Serial No.: 0115	12-Jul-1999 Glaxo Wellcome Correspondence
lrochloride) lequest	General Correspondence
	Clinical Meeting Request
	0115

Protocol: S3BA3001, S3BA3003

IND 48,487		14-Jul-1999 Glaxo Wellcome Correspondence	
IND 48,487: GR68755 Tablets (alosetron hydrochloride)	-	come Correspondence	
	Protocol Amendment: New Investigator	Protocol Amendment: New Protocol	
	Investigator Add	Investigator Add	
		0116	

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Serial No.: 0116

Regulatory Affairs CARDS

44 09:47:32

Chronology

LAM78906

23-Mar-2000

Application: Date Range: Date ΑII N Communication Type 48487; GR68755 Tablets (alosetron hydrochloride) Document Type Document Subtype Serial / Supp #

22-Jul-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Investigator Add 0117

Investigator: Archambault, Andre, Beckwith, Jay G, Bursey, Ronald Ford, Drossman, Douglas A, Fidelholtz, James I, Scholz, David George, Winston, Barry D, Zanten, Sander Van

Serial No.: 0117

05-Aug-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change Investigator Add 0118

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator

Serial No.: 0118

Protocol: S3B30004, S3B30006, S3BA3003

Protocol with Investigator(s):

S3B20015 with: Alan Plotner, M.D.

11-Aug-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Protocol Amendment: New Protocol Investigator Add 0119

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol Protocol Amendment: New Investigator

Serial No.: 0119

Protocol with Investigator(s):

S3B30011 with:

Chester L. Fisher, Jr., M.D.

· 18-Aug-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change 0120

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

LAM78906

23-Mar-2000

Regulatory Affairs

Chronology **CARDS**

45 09:47:32

Application: A B

48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

Date Communication Type Protocol Amendment: New Investigator

Document Type

Document Subtype

Serial / Supp #

Serial No.: 0120

Protocol: S3B20015, S3BA3003

19-Aug-1999 Glaxo Wellcome Correspondence

Manufacturing and Controls Information Amendment: Chemistry

CMC

0121

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Information Amendment: Chemistry Manufacturing and Controls, CMC

Serial No.: 0121

01-Sep-1999 Glaxo Wellcome Correspondence

Manufacturing and Controls Information Amendment: Chemistry

CMC

0122

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Information Amendment: Chemistry Manufacturing and Controls, CMC

Serial No.: 0122

08-Sep-1999

Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator Investigator Add

Other 1572 Change

0123

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator

Serial No.: 0123

Protocol: S3B20015, S3B30006, S3BA3003

Protocol with Investigator(s):

S3B30011 with:

E Lucas, D.O., Michael A McAdoo, M.D., Jerry L Miller, M.D., Lanning R Newell, M.D., Gary E Poleynard, M.D., J Mark Provenza, M.D., Kenneth W Rioctor, M.D., Steven E Roberts M.D., Michael A Rosemore, M.D., Eric S Solomon, M.D., Malcolm J. Sperling, M.D., Kenneth R. W. Warren, M.D., James L Williams II, M.D., Douglas Young, M.D. M.D., Park T Chittom, M.D., Frank N. Cole, M.D., Kathleen L Collins, M.D., William Thomas Garland, M.D., Nazim Jaffer, M.D., Richard B Jonas, M.D., Richard E Lassiter, M.D., Mel Lawrence K. Alwine, M.D., Marcelo A Barreiro, M.D., Charles I Biltz, M.D., Lee M Carter, M.D., Charles J Cattano, M.D., F.A.C.P., John J Champlin, M.D., Christopher M. Chappel,

23-Mar-2000 LAM78906 Chronology CARDS

Application: AI N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

14-Sep-1999 Date Glaxo Wellcome Correspondence Communication Type Protocol Amendment: New Investigator Document Type Protocol Amendment: New Protocol Investigator Add Document Subtype

Amendment: Other

Research Organization

Transfer of Obligations to Contract

Serial / Supp #

46 09:47:32

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Amendment: Other, Transfer of Obligations to Contract Research Organization

Serial No.: 0124

Protocol with Investigator(s):

S3B30012 with:

Marcelo A Barreiro, M.D.

Protocol with Report(s):

S3B30012 with:

RC1999/00003/00

Comment: IBAH, Four Valley Square, 512 Township Line Rd., Blue Bell, PA 19422

15-Sep-1999 Glaxo Wellcome Correspondence Serial No.: 0125 10-Day ADR Report: Follow-up IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Follow-up

0125

Protocol: S3BB3001

ADR: B0062540A

15-Sep-1999 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Initial 0126

Protocol: S3BB3002

Serial No.: 0126

10-Day ADR Report: Initial

ADR: B0070392A

17-Sep-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Investigator Add 0127

CARDS Chronology

09:47:32

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: All

LAM78906

23-Mar-2000

Date Communication Type Document Type Document Subtype Serial / Supp #

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator

Protocol with Investigator(s):

Serial No.: 0127

S3B30011 with:

Charles W White, Sr., M.D., Gregory J Wiener, M.D., Steven Wilson, M.D. Koch, M.D., Michael J McCarmey, M.D., Jeffrey R Medoff, M.D., FACG, Paul Hooper Nichols, M.D., Larry R Popeil, M.D., FAAFP, Albert J Razzetti, M.D., Adisesha B Reddy, M.D., Mario Z Rosenberg, M.D., Valeria A Scott, M.D., William N Sokol, Jr., M.D., Randall R. Stoltz, M.D., Gregg A Valenzuela, M.D., Arthur S Waldbaum, M.D., Colin L Walker, M.D., Dahdul, M.D., Mark I DeBruin, D.O., Ronald G DeGarmo, D.O., Hugh D Durrence, M.D., Ronald D Emkey, M.D., FACP, James T. Farrell, D.O., Edwin B Flanagan, D.O., Mark S. Fraley, D.O., Kathryn G Gilliland, M.D., David R Hassman, D.O., John A. Jernigan, M.D., John F Johanson, M.D., Neil M Kassman, M.D., Lionel Bernard Katchem, D.O., PC, Milton J Steven M Adkins, M.D., Louis V Antignano, M.D., Allan B Aven, M.D., Joan Ryder Benz, M.D., Eileen M Brady, M.D., Robert E. Broker, M.D., Robert G Cesarec, M.D., Adnan

2	Static Undate	General Teleconference	28 San 1999 Food and Days Administration Telephone	28 San 1000
			General Teleconference	
		ochloride)	IND 48,487; GR68755 Tablets (alosetron hydrochloride)	
	Request Status Update			
	Protocol			
	Nonclinical			
	CMC			
	Clinical	General Teleconference	17-Sep-1999 Glaxo Wellcome Telephone Conversation	17-Sep-1999

29-Sep-1999 Glaxo Wellcome Correspondence Protoco	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Status Update	28-Sep-1999 Food and Drug Administration Telephone General Conversation
Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol		General Teleconference
Clinical		Status Update
0128		

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator

Investigator Add

CARDS

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23-Mar-2000 LAM78906 Chronology

Application: IND Date Range: All 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Protocol Amendment: New Protocol Document Type Document Subtype Serial / Supp #

Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator

Serial No.: 0128

Protocol: S3B20023

Protocol with Amendment(s):

S3B20023 with:

Protocol with Investigator(s): S3B20023 with:

R Bruce Johnson, M.D.

30-Sep-1999

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: Change in Protocol

Serial No.: 0129

Protocol with Amendment(s):

S3B10906 with:

S3B20015 with:

S3B30006 with:

S3BA1006 with:

Protocol with Report(s):

S3B10906 with:

NN1999/00052/01

S3B20015 with:

RM1998/00464/03

GM1998/00349/01 S3B30006 with:

S3BA1006 with:

NN1998/00001/02

Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol Clinical 0129

Chronology CARDS

Application: N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

23-Mar-2000 LAM78906

Date Glaxo Wellcome Correspondence Communication Type Document Type 10-Day ADR Report Follow-up Document Subtype Serial / Supp #

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

10-Day ADR Report: Follow-up

Serial No.: 0130

Protocol: S3BB3002 ADR: B0070392A

01-Oct-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0131

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator

Serial No.: 0131

Protocol with Investigator(s):

S3B30004 with:

William Y Chey, M.D.

S3B30006 with:

Arthur Green, D.O., Bruce Jones, M.D.

S3B30011 with:

Simon, M.D., J Christopher Stringer, M.D., Steven L Thomason, M.D., Michael U Todd, M.D., Monte E Troutman, D.O., Jonathan S Wechsler, D.O., L Michael Weiss, M.D., David J Gregory M Mula, M.D., John D Nuschke, M.D., Ralph Steven Pulverman, D.O., Marina Raikhel, M.D., Robert B Rhoades, M.D., Scott P Sainburg, M.D., Barry Michael Schultz, M.D., Wenzel, M.D., Barry D Winston, M.D., Robert J Ziltzer, M.D. Jerrold Lloyd Schwartz, M.D., William M Seger, M.D., Umedchandra K Shah, M.D., Joseph Neville Shepherd, Jr., M.D., Gerard V Siciliano, M.D., Ann L Silverman, M.D., James A James A Krug, M.D., Mark Eliot Kutner, M.D., Daniel Henri Laury, M.D., Lawrence S Levinson, M.D., Robert Darryl Marks, M.D., George T Maughan, M.D., Frank Mazzone, M.D., M.D., Robert Hardi, M.D., Richard E Hedrick, Jr., M.D., Timothy M Howard, M.D., Stephen L Ionna, M.D., Neil M Kassman, M.D., Ross A Kommor, M.D., William F Korcek, M.D., Monique Forred, M.D., John D Gabriel, M.D., David B George, M.D., Harvey A Giller, M.D., Michael W Gorsky, M.D., Louis J Gringeri, M.D., Frances F Haas, M.D., David Harari, F.A.C.P., Richard Charles Coalson, M.D., Teresa L Coats, M.D., William Randall Cox, M.D., William A Daniel, M.D., Robert A Davenport, M.D., Enrique Carlos M. De Castro, M.D., Kevin Howard Ashby, M.D., Charles A Birbara, M.D., Mark David Blitstein, M.D., Michael L Bloom, M.D., Fred A Brosco, M.D., John A Brose, M.D., Charles J Cattano, M.D., David W Dozer, M.D., John J Eck, M.D., Atilla Ertan, M.D., Robert A Feldman, M.D., Jeffrey D Feldstein, M.D., Scott D Fenske, M.D., Don S Fixler, M.D., Ronald A Ford, M.D., Marie

S3B30012 with:

Paula A Crenshaw, M.D., Todd J Hammer, M.D., Jeffrey R Herbst, M.D., Annette R Hull, M.D., Rajeev K Jain, M.D., Mohammad Nadeemullah, M.D., Kristine D Weiss, M.D.

'Charles K Bedard, M.D., Roland William Bennetts, M.D., Philip C Bird, M.D., William H Holderman, M.D., David A Johnson, M.D., Chester W Kessler, M.D., Thomas LoIudice, DO, James McGill, M.D., Alan Plotner, M.D., Stephen C Schindler, M.D., Charles W Scrowcroft, M.D., Steven J Wegley, M.D., James D Wolosin, M.D.

09:47:32

CARDS

23-Mar-2000 LAM78906 Chronology 50 09:47:32

Application: IND
Date Range: All 48487; GR68755 Tablets (alosetron hydrochloride)

0132	Investigator Add	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	01-Oct-1999 Glaxo Wellcome Correspondence	01-Oct-1999
Serial / Supp #	Document Subtype	Document Type	Communication Type	Date

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Serial No.: 0132

Protocol: S3B10935

Protocol with Investigator(s):

S3B10935 with:

Philip T Leese, M.D.

	04-Oct-1999	
	04-Oct-1999 Glaxo Wellcome Correspondence	
	Annual Report	
Changes to Investigator's Brochure Clinical Study Information CMC Investigational Plan Outstanding Regulatory Business	Adverse Event Summary	
	0133	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Annual Report

Serial No.: 0133

Comment: Period Covering: August 5, 1998 - August 4, 1999 Protocol: S3B20012, S3B20013, S3B20015, S3B30004, S3B30006, S3BA1001, S3BA1002, S3BA1004, S3BA1006, S3BA2002, S3BA3001, S3BA3002, S3BA3003, S3BB2011

08-Oct-1999 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0134

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0134

Protocol with Investigator(s):

'S3B20015 with:

Roland William Bennetts, M.D., Scott D Bleser, D.O., Richard A Krause, M.D., Michael Safdi, M.D., David George Scholz, M.D.

\$3B30006 with:

CARDS

23-Mar-2000 LAM78906 Chronology

09:47:32

Date Range: Application: 48487; GR68755 Tablets (alosetron hydrochloride)

Fabio Cominelli, M.D., James I Fidelholtz, M.D., Chester W Kessler, M.D., Kichard A Krause, M.D., S Jon Mason, M.D., William S Mullican, M.D., David J Sales, M.D., Gerald D Date Communication Type Document Type Document Subtype Serial / Supp #

Wolfley, M.D.

S3B30011 with:

M.D., Robert L Pintozzi, M.D., Bryan C Pogue, M.D., James C Pollock, M.D., Charles Wilson Randall, M.D., Dennis A Ruff, M.D., Mark P Runde, M.D., Frederick N Shuler, M.D., G Gilbert Ledesma, M.D., Stefan P Marcuard, M.D., Thomas E Melchione, M.D., James M Mertesdorf, M.D., Sam E Moussa, M.D., Diane M Normandin, M.D., Thomas Francis O'Meara, Lawrence D Wruble, M.D. Scott Smith, M.D., Richard N Steller, M.D., Patricia A Stephenson, M.D., Joanna K Tan, M.D., John Jerome Upchurch, M.D., Vincent F Vacca, M.D., Steven I Wilkofsky, M.D., Daniel E Gremillion, M.D., James R Hill, M.D., Reed Blanchard Hogan, II, M.D., Isaac Kalvaria, M.D., James R Kelly, M.D., M.B.A., David G Kohm, M.D., Elliot Joseph Kopp, M.D., Davenport, M.D., Jeffrey J Dorociak, M.D., Ph.D., R David Ferrera, M.D., Jeffrey J Glass, M.D., S.C., Carl Allen Goetsch, M.D., Stanley B Goldberg, M.D., Michael J Goldstein, M.D., Jay L Adler, M.D., Ajit S Arora, M.D., Michael P Basista, M.D., Parth S Bharill, M.D., Frederick A Bieberdorf, M.D., Robert L Brannon, M.D., Paul Martin Craig, M.D., Robert A

S3B30012 with:

M.D., G Wynne Stubbs, M.D., Eric N Zacharias, M.D. Craig A Ennis, M.D., William F Erfling, M.D., John T Foss, M.D., R William Hilty, M.D., William D Koltun, M.D., Joseph V Marino, M.D., Gayle S Moyer, M.D., William A Spisak,

S3BA3003 with:

Michael G DeLissio, M.D., Martin D Gelfand, M.D., Arthur Green, D.O., Dennis C. McCluskey, M.D., William S Mullican, M.D

12-Oct-1999 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Initial 0135

10-Day ADR Report: Initial

Serial No.: 0135

ADR: A0102342A Protocol: S3B20015

15-Oct-1999 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0136

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0136

Protocol with Investigator(s)

S3B20023 with:

1 Golding, M.D., Michael R Grossman, M.D., Paula H Hall, M.D., E Walter Hood, M.D., David S James, DO, John J Jolley, M.D., James H Linne, M.D., Robert Darryl Marks, M.D., S3B30006 with: Philip B Miner, M.D., Daniel J Pambianco, M.D., David S Schulman, M.D., William R Stern, M.D. Michael T Bennett, M.D., Scott D Bleser, D.O., Milan Brandon, M.D., Michael E Brewer, Ph.D., M.D., Eugene J Burbige, M.D., Michael F Elmore, M.D., Syam P Gaddam, M.D., Martin

Chronology **CARDS**

Application: 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

23-Mar-2000 LAM78906

Vermon G.K. Hee, M.D. Date Communication Type

S3B30011 with:

Fogel, M.D., Michael M Gaspari, M.D., David R Greenberg, D.O., Laurie S Haas, M.D., Marvin A Heuer, M.D., Scott Ingber, M.D., Hymie Kavin, M.D., Nicholas A Knight, M.D., Kevin K Koffel, M.D., Lynda Beth Milligan, M.D., Joseph P Moore, M.D., Gayle S Moyer, M.D., Joy Schechtman, D.O., G Scott Smith, M.D., Dale A Sundwall, M.D., FACOG, Richard Larry A Adler, M.D., Roger C Anderson, M.D., Joel I Bessoff, M.D., William C Bray, M.D., David C Chua, M.D., Margaret A. Drehobl, M.D., Samuel W Flannagan, M.D., Ronald

Document Type

Document Subtype

Serial / Supp #

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A Truesdale, Jr., M.D., John C Turse, M.D., Michael D Van Norstrand, M.D., John M Wadleigh, D.O., Richard A Wright, M.D., Barbara K Zedler, M.D.

S3B30012 with:

M.D. Larry A Adler, M.D., Paul I Berkowitz, M.D., David D Campbell, M.D., Frank S Eder, M.D., John J Giannone, M.D., Gregory M Knopf, M.D., Robert H Levine, M.D., Daniel M Young

S3BA3003 with:

Oscar Oandasan, M.D.

15-Oct-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Protocol Amendment: New Protocol Amendment: Other Transfer of Obligations to Contract Investigator Add 0137

Research Organization

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Amendment: Other, Transfer of Obligations to Contract Research Organization

Serial No.: 0137

Protocol with Investigator(s):

S3B30013 with:

Scott D Bleser, D.O.

Protocol with Report(s):

S3B30013 with:

RM1999/00195/00

Comment: ICON Clinical Research, 115 East park Drive, Suite 200, Brentwood, TN 37027

20-Oct-1999 Glaxo Wellcome Correspondence

Protocol Amendment: New Protocol

Amendment: Other Protocol Amendment: New Investigator

Transfer of Obligations to Contract Investigator Add

0138

Research Organization

Protocol Amendment: New Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride)

CARDS

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Date Range: Application: AII D 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Document Subtype

Serial / Supp #

Serial No.: 0138

Amendment: Other, Transfer of Obligations to Contract Research Organization

Protocol Amendment: New Investigator

Protocol with Investigator(s):

S3B10939 with:

Philip T Leese, M.D.

Protocol with Report(s):

S3B10939 with:

NN1999/00080/00

Comment: Quintiles, Inc., 1007 Slater Rd., Chelsea Place, Durham NC 27703

22-Oct-1999 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Manufacturing and Controls Information Amendment: Chemistry CMC

0139

Information Amendment: Chemistry Manufacturing and Controls, CMC

Serial No.: 0139

25-Oct-1999

Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Protocol Amendment: New Protocol Transfer of Obligations to Contract Investigator Add

Amendment: Other

Research Organization

0140

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Amendment: Other, Transfer of Obligations to Contract Research Organization

Serial No.: 0140

Protocol: S3B10937

Protocol with Investigator(s):

S3B10937 with:

Philip T Leese, M.D.
Protocol with Report(s):

S3B10937 with:

Chronology CARDS

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Date Range: Application: All IND 48487; GR68755 Tablets (alosetron hydrochloride)

23-Mar-2000 LAM78906

00/8/000/6661NN Date Communication Type Document Type Document Subtype Serial / Supp #

Comment: Quintiles, Inc., 1007 Slater Road, Chelsea Place, Durham, NC 27703

26-Oct-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other Transfer of Obligations to Contract Investigator Add 0141

Research Organization

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Amendment: Other, Transfer of Obligations to Contract Research Organization

Serial No.: 0141

Protocol: S3B10936

Protocol with Investigator(s):

S3B10936 with:

Philip T Leese, M.D.

Protocol with Report(s):

S3B10936 with:

NN1999/00077/00

Comment: Quintiles, Inc., 1007 Slater Road, Durham, NC 27703

28-Oct-1999 Glaxo Wellcome Correspondence 10-Day ADR Report Follow-up 0142

10-Day ADR Report: Follow-up IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0142

ADR: A0102342A Protocol: S3B20015

29-Oct-1999 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol Clinical 0143

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol

Serial No.: 0143

Chronology **CARDS** 55 09:47:32

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: ΑII

LAM78906 23-Mar-2000

S3BA3003 with: Protocol with Amendment(s):

Date Communication Type

Document Type

Document Subtype

Serial / Supp #

S3BA3003 with: RM1997/00540/07 Protocol with Report(s):

01-Nov-1999 Glaxo Wellcome Correspondence 10-Day ADR Report Follow-up

0144

Serial No.: 0144 10-Day ADR Report: Follow-up

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

ADR: A0070339A Protocol: S3BA3001

01-Nov-1999 Glaxo Wellcome Correspondence

10-Day ADR Report

Follow-up

0145

10-Day ADR Report: Follow-up

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0145

Protocol: S3BA3003

ADR: A0067942A

05-Nov-1999 Glaxo Wellcome Correspondence

General Correspondence

Other

0146

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Correspondence: PROPOSED PEDIATRIC STUDY REQUEST

Serial No.: 0146

Protocol: S3B10903, S3B10934, S3B30015, S3B30016, S3B30018, S3B30019

11-Nov-1999 Glaxo Wellcome Correspondence 10-Day ADR Report

Follow-up

0147

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

10-Day ADR Report: Follow-up

Serial No.: 0147

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Date Range: Application: 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Document Subtype Serial / Supp #

Protocol: S3B20015 ADR: A0102342A

12-Nov-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change Investigator Add

0148

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0148

Protocol with Investigator(s)

William Y Chey, M.D., W. Travis Ellison, M.D., Paul J Lebovitz, M.D., Shahriar S Safavi, M.D.

S3B20023 with:

D Wolosin, M.D. Sales, M.D., Michael Johannes Schmalz, M.D., Colleen M Schmitt, M.D.MHS, Howard I. Schwartz, M.D., Ronald Schwarz, M.D., Robert E Tepper, M.D., Ellis E Williams, M.D., James DO, Gregory D Mackay, M.D., Douglas H Orchard, M.D., Ronald E Pruitt, M.D., Joseph Reddy, M.D., Harvey Resnick, M.D., Sidney Rosenblatt, M.D., Michael Safdi, M.D., David J D. Klein, M.D., Ross A Kommor, M.D., Steven Krumholz, M.D., Michael Kurtz, M.D., Charles W Laudenbach, M.D., Jake C Lennard, M.D., Mark L Lloyd, M.D., Thomas Loludice, Goetsch, M.D., Mark G Griffin, M.D., Robert K Hippert, D.O., Robert Holmes, M.D., R Bruce Johnson, M.D., Bruce Jones, M.D., Boris Kerzner, M.D., Chester W Kessler, M.D., Terry Michael G DeLissio, M.D., Thomas N Dewar, M.D., Ben J Dolin, M.D., John K Earl, M.D., Jeffrey P Fenyves, M.D., Fred C Fowler, M.D., Kevin T Geraci, M.D., FACP, Carl Allen Hector D Allende, M.D., Clifford J Appel, M.D., Charles Franklin Barish, M.D., Mark David Blitstein, M.D., Elizabeth S Bray, M.D., Jeffrey R Breiter, M.D., Lawrence B Cohen, M.D.,

S3B30006 with:

Karna Dev Bardhan, M.D., William R. Berry, M.D., Robert M Finlaw, M.D., Antony Barnabas Hawthorne, M.D., Anna Maclean, M.D., Stephen M Schindler, M.D., James R Wagner,

S3B30011 with:

McNeil, D.O., Radman Mostaghim, M.D., Michael I Nissensohn, M.D., Thomas Rosenfield, M.D., Stuart M Topkis, D.O. Simmy S Bank, M.D., Parth S Bharill, M.D., John W Birk, M.D., William H Bobbitt, III, M.D., Alvan E. Fisher, M.D., Marie Monique Forred, M.D., Dale P McGinty, M.D., Harold G

S3B30012 with:

'Whatley, M.D., Barry D Winston, M.D., Lawrence D Wruble, M.D., Gary D Yeoman, D.O., Frank A Zazueta, M.D. W Schnure, M.D., Howard I. Schwartz, M.D., Michael E Schwartz, D.O., Randall J Severance, M.D., Dirk P Slaker, M.D., Martin L Throne, M.D., David M Turner, M.D., James C Joseph W Baker, M.D., Brian Thomas Bock, D.O., David S Brandenburg, M.D., Shari Anne Brazinsky, M.D., C Don Bryant, M.D., Francesco Cabrera, M.D., James P Capo, Jr., M.D., Billy G Chacko, M.D., Murray H Cohen, D.O., Martin J Drost, M.D., David S Friedman, D.O., Glenn D Gafford, M.D., Timothy J Gardner, M.D., Harry I. Geisberg, M.D., Jeffrey G Nichols, M.D., John P Pasquariello, Jr., M.D., R Walter Powell, M.D., Mark K Radbill, D.O., Michele Reynolds, M.D., Janelle A Rhyne, M.D., FACP, Bruce A Salzberg, M.D., Frederick DTM & H, Rokay Kamyar, M.D., Joseph William Kittinger, III, M.D., FACP, Eric J Klein, M.D., Scott H Lieberman, M.D., William E Lyles, M.D., David M Maccini, M.D., Keith A Geohas, M.D., Harold Guy, M.D., Duane J Henk, M.D., Marvin A Heuer, M.D., David N Holt, M.D., Kevin D Inwood, M.D., George Whitfield James, M.D., Paul F Kamitsuka, M.D.,

Hector D Allende, M.D., Clifford J Appel, M.D., Charles Franklin Barish, M.D., Jim Bauer, M.D., John W Beckman, M.D., Michael T Bennett, M.D., Milan Brandon, M.D., Elizabeth S

23-Mar-2000 LAM78906 Chronology CARDS

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Application: Date Range: ΑII 48487; GR68755 Tablets (alosetron hydrochloride)

M.D., Stephen C Schindler, M.D., David S Schulman, M.D., David B Stanton, M.D., Ellis E Williams, M.D., James D Wolosin, M.D. Kessler, M.D., Steven Krumholz, M.D., Jake C Lennard, M.D., James H Linne, M.D., Robert Darryl Marks, M.D., Daniel J Pambianco, M.D., Sidney Rosenblatt, M.D., Michael Safdi, M.D., Michael R Grossman, M.D., Paula A Hall, M.D., Curtis Scott Horn, M.D., Sima G Issen, M.D., David S James, DO, R Bruce Johnson, M.D., John J Jolley, M.D., Chester W Bray, M.D., Jeffrey R Breiter, M.D., Michael E Brewer, Ph.D., M.D., Eugene J Burbige, M.D., Lawrence B Cohen, M.D., Selwyn A Cohen, M.D., Michael T Draelos, M.D., Michael F Elmore, M.D., Jeffrey P Fenyves, M.D., Fred C Fowler, M.D., David Gabbaizadeh, M.D., Syam P Gaddam, M.D., Kevin T Geraci, M.D., FACP, Oliver D Gilliam, M.D., Mark G Griffin Date Communication Type Document Type Document Subtype Serial / Supp #

Murray, M.D., Jansi Prabakaran, M.D., Patricia Raymond, M.D., Mario Z Rosenberg, M.D., Douglas Schumacher, M.D., Ronald Schwarz, M.D., Richard A Wright, M.D. Jacques R. Caldwell, M.D., Charles L Colip, M.D., Raquel Croitoru, M.D., Robert M Finlaw, M.D., Michael R Grossman, M.D., Robert Holmes, M.D., George Koval, M.D., Linda P S3BA3003 with:

18-Nov-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Clinical Investigator Add

0149

Research Organization Transfer of Obligations to Contract

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Amendment: Other, Transfer of Obligations to Contract Research Organization

Protocol Amendment: Change in Protocol

Serial No.: 0149

Protocol with Investigator(s):

S3B10938 with:

Philip T Leese, M.D

18-Nov-1999

Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Amendment: Other

Change in Medical Monitor Investigator Add

0150

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0150

Protocol: S3B30013

Protocol with Investigator(s):

S3B20023 with:

Shane Agnew, M.D., FRCP(C), Michel Boivin, M.D., Uduma Kalu, M.D., M.Sc., FRCP, Edwin Larkai, M.D., Gaetano Morelli, M.D., FRCP, Alan Thomson, M.D., M.S.C., Ph.D., S3B30013 with:

Shane Agnew, M.D., FRCP(C), Michel Boivin, M.D., Uduma Kalu, M.D., M.Sc., FRCP, Edwin Larkai, M.D., Joseph Loutfi, M.D., Gaetano Morelli, M.D., FRCP

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Date Range:

Application:

23-Mar-2000 LAM78906

48487; GR68755 Tablets (alosetron hydrochloride)

Date

Communication Type

Document Type

Document Subtype

Serial / Supp #

Comment: Christine Marie Hunt, M.D., F.A.C.P.

29-Nov-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change Investigator Add 0151

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator

Serial No.: 0151

Protocol with Investigator(s)

Ronald Schwarz, M.D., Richard White, M.D.

Compton, M.D., Gordon T Connor, M.D., W. Travis Ellison, M.D., Michael S Epstein, M.D., Gulchin A Ergun, M.D., Duane D Fitch, M.D., David L Fried, M.D., Gregory Fusilier, M.D., Oliver D Gilliam, M.D., William R Harlan, III, M.D., William H Holderman, M.D., Curtis Scott Horn, M.D., Spencer B Jones, M.D., Donald G Kaufman, M.D., Douglas W Kirtley, M.D., Ira E Stein, M.D., James G Sullivan, M.D., William H Taub, M.D., John A Walker, M.D., Strick J Woods, M.D. M.D., Gary E Poleynard, M.D., Lance A Rudolph, M.D., Michael D Schiff, M.D., Charles J Sigmund, M.D., Thomas J Sobieski, III, M.D., David B Stanton, M.D., Bruce E Stein, M.D., Jack A Klapper, M.D., Richard A Krause, M.D., Michael S Levine, M.D., Hari N Malik, M.D., David G Mangels, M.D., David J Morin, M.D., William J O'Toole, M.D., Jacob L Pinnas, Kevin Howard Ashby, M.D., J Luis Bautista, M.D., John W Beckman, M.D., Thomas D Bianchi, M.D., Steven K Brodie, M.D., Nicholas W Cirillo, D.O., Selwyn A Cohen, M.D., Rand F

S3B30006 with:

Oliver D Gilliam, M.D., Vernon G.K. Hee, M.D., Steven Krumholz, M.D., William S Mullican, M.D.

S3B30011 with:

Howard, M.D., Ross A Kommor, M.D., Gary E Poleynard, M.D., Larry R Popeil, M.D., FAAFP Parth S Bharill, M.D., Charles I Biltz, M.D., John A Brose, M.D., Lee M Carter, M.D., William Randall Cox, M.D., Ronald D Emkey, M.D., FACP, James R Hill, M.D., Timothy M.

S3B30012 with:

S3B30013 with: Kim, M.D., William E Lyles, M.D., Thomas Francis O'Meara, M.D., Dennis Pangtay, M.D., Andres Patron, Marina Raikhel, M.D., Michael E Schwartz, D.O., Frank A Zazueta, M.D. Malek H Al-Omary, M.D., Shari Anne Brazinsky, M.D., Hubert S Gaskin, III, M.D., Harold Guy, M.D., Randall T Huling, M.D., Harold Isenberg, M.D., Robert M Karns, M.D., David O

M.D., Michael D Schiff, M.D., Michael Johannes Schmalz, M.D., Colleen M Schmitt, M.D.MHS, David Jay Schneiderman, M.D., FACS, Howard I. Schwartz, M.D., Ronald Schwarz, Douglas H Orchard, M.D., Peter M Pardoll, M.D., Jacob L Pinnas, M.D., Joseph Reddy, M.D., Harvey Resnick, M.D., Lance A Rudolph, M.D., Shahriar S Safavi, M.D., James A Sattler, M.D., Ira E Stein, M.D., James G Sullivan, M.D., William H Taub, M.D., Robert E Tepper, M.D., Gerald D Wolfley, M.D., Strick J Woods, M.D. Lebovitz, M.D., Thomas Loludice, DO, N Martin Lunde, M.D., Gregory D Mackay, M.D., David G Mangels, M.D., Philip B Miner, M.D., David J Morin, M.D., Joseph L Nelson, M.D., Fisher, M.D., Duane D Fitch, M.D., Ronald Fogel, M.D., Gregory Fusilier, M.D., Robert K Hippert, D.O., Jack A Klapper, M.D., Richard A Krause, M.D., Michael Kurtz, M.D., Paul J Steven K Brodie, M.D., Nicholas W Cirillo, D.O., Michael G DeLissio, M.D., Thomas N Dewar, M.D., Ben J Dolin, M.D., Michael S Epstein, M.D., Gulchin A Ergun, M.D., Richard

Rokay Kamyar, M.D., Richard A Krause, M.D., Herbert Rubin, M.D., Craig W Wiesenhutter, M.D.

CMC

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Application: N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: All

Date

23-Mar-2000 LAM78906

Communication Type Manufacturing and Controls Document Type Document Subtype

Serial / Supp #

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Protocol Amendment: New Investigator Protocol Amendment: New Protocol Investigator Add

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Information Amendment: Chemistry Manufacturing and Controls

Protocol Amendment: New Protocol: PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY

Protocol Amendment: New Investigator

Serial No.: 0152

Protocol with Investigator(s):

S3B10903 with:

Gregory L Kearns, Pharm.D

S3B10934 with:

Gregory L Kearns, Pharm.D.

Protocol with Report(s):

S3B10903 with: NN1999/00069/00

S3B10934 with:

NN1999/00070/00

01-Dec-1999 Glaxo Wellcome Correspondence Amendment: Other Protocol Amendment: New Protocol Research Organization Transfer of Obligations to Contract 0153

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Amendment: Other, Transfer of Obligations to Contract Research Organization

Serial No.: 0153

Protocol: S3B30020

Protocol with Report(s):

S3B30020 with:

RC1999/00013/00

Comment: Quintiles, Inc., 1007 Slater Rd., Chelsea Place, Durham, NC 27703

08-Dec-1999 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change Investigator Add 0154

CARDS

23-Mar-2000 LAM78906 Chronology

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Date Range: Application: 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Document Subtype Serial / Supp #

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol with Investigator(s)

Serial No.: 0154

S3B20023 with:

M.D., Marc J Zuckerman, M.D. Paul E Brown, M.D., Sudhir K Dutta, M.D., Vernon G.K. Hee, M.D., John F Johanson, M.D., Bernard King, M.D., Desmond Leddin, M.D., Robert D Lerner, M.D., Scot Michael Lewey, Prest, M.D., FRCP(C), Lee R Rocamora, M.D., Shahriar S Safavi, M.D., James A Sattler, M.D., Eugene Spiotta, M.D., Ellis E Williams, M.D., John A Winder, M.D., John D Zander, D.O., N Martin Lunde, M.D., Gaetano Morelli, M.D., FRCP, William S Mullican, M.D., Peter M Pardoll, M.D., William Paterson, M.D., FRCP(C), Bennett H Plotnick, M.D., Marcia

S3B30011 with:

Steven M Adkins, M.D., Kathleen L Collins, M.D.

S3B30012 with:

Richard D. Baerg, M.D., Dale M Carter, M.D., Robert John Koval, M.D., David Raul Munoz, M.D., Steven L Nack, M.D., Julio E Navarro, M.D.

S3B30013 with:

FRCP(C), Donato Ricci, M.D., Thomas J Sobieski, III, M.D., James D Torosis, M.D., Lawrence D Wruble, M.D., John D Zander, M.D., Robert M. Zuckerman, M.D. Bryan L Magenheim, M.D., Dennis C. McCluskey, M.D., William J O'Toole, M.D., Naynesh Patel, M.D., William Paterson, M.D., FRCP(C), Alan Plotner, M.D., Marcia Prest, M.D., M.D., Steven Krumholz, M.D., Edwin Larkai, M.D., Ben George Lazarus, D.O., Desmond Leddin, M.D., Robert D Lerner, M.D., Michael S Levine, M.D., Robert L Lindenberg, M.D., Mark Atin, FRCP(C), Jim Bauer, M.D., J Luis Bautista, M.D., Thomas D Bianchi, M.D., Mark David Blitstein, M.D., D Eric Bolster, M.D., Paul E Brown, M.D., David L Fried, M.D., Carl Allen Goetsch, M.D., John Sawyer Goff, M.D., William H Holderman, M.D., Adesh K Jain, M.D., Thomas K Judd, M.D., Boris Kerzner, M.D., Bernard King, M.D., Terry D. Klein,

S3BA3003 with:

Sudhir K Dutta, M.D., Charles D Hanshaw, M.D., David A Johnson, M.D., Linda P Murray, M.D., Thomas J Pulliam, M.D., Patrick Schow, M.D., M. Scott Touger, M.D.

0155

09-Dec-1999 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Amendment: Other Protocol Amendment: Change in Protocol Protocol Amendment: New Protocol Research Organization Clinical Transfer of Obligations to Contract

Protocol Amendment: New Protocol: PEDIATRIC PROTOCOLS SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY

Protocol Amendment: Change in Protocol

Serial No.: 0155 Amendment: Other, Transfer of Obligations to Contract Research Organization

' Protocol with Amendment(s): S3B30012 with:

CARDS

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Application: 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range:

Date Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol with Report(s):			
S3B30012 with:			
PC1000/0003/01			

S3B30015 with: RM1999/00324/00 RC1999/00003/01

S3B30019 with:

RM1999/00327/00

Comment: ICON Clinical Research, 1110 W. Lake Cood Road, Suite 220, Buffalo Grove, IL 60089

15-Dec-1999 Glaxo Wellcome Correspondence Protocol Amendment: Change in Protocol Clinical 0157

Protocol Amendment: Change in Protocol IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0157

S3B30020 with: Protocol with Amendment(s):

S3B30020 with: Protocol with Report(s):

RC1999/00013/01

15-Dec-1999 Glaxo Wellcome Correspondence 10-Day ADR Report Initial Follow-up 0156

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

10-Day ADR Report: Initial

Serial No.: 0156

Protocol: S3B30011 ADR: A0107106A

	21-Dec-1999 GI	
	Glaxo Wellcome Correspondence	
	Protocol Amendment: New Investigator	
Other 1572 Change	Investigator Add	
	0158	

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0158

Chronology CARDS

09:47:32

Application: Date Range: All 48487; GR68755 Tablets (alosetron hydrochloride)

23-Mar-2000 LAM78906

Document Type

Document Subtype

Serial / Supp #

Date Communication Type

James I Fidelholtz, M.D

Protocol with Investigator(s)

S3B30006 with: Kommor, M.D., Paul J Lebovitz, M.D., Robert L Lindenberg, M.D., Donald E Loew, M.D., Pierre Pare, M.D., Naynesh Patel, M.D., Frederick N Shuler, M.D., Richard White, M.D. Ph.D., Michael T Draelos, M.D., Ronald Fogel, M.D., Robert M Gannan, M.D., John Sawyer Goff, M.D., Paula A Hall, M.D., Adesh K Jain, M.D., Thomas K Judd, M.D., Ross A M Angeli Adamczyk, M.D., Kevin Howard Ashby, M.D., Gary M Barton, M.D., Charles K Bedard, M.D., Chrystian Dallaire, M.D., FRCP, CSPQ, Ghhislain Devroede, M.D., MSc.

S3B30011 with: David A Johnson, M.D., Robert L Lindenberg, M.D., Denis M McCarthy, M.D., David J Sales, M.D., Stephen C Schindler, M.D., Charles J Sigmund, M.D., Craig W Wiesenhutter, M.D.

Mostaghim, M.D., Steven E Roberts, M.D., Richard A Truesdale, Jr., M.D., Jonathan S Wechsler, D.O., James L Williams II, M.D. Allan B Aven, M.D., Margaret A. Drehobl, M.D., David R Hassman, D.O., Neil M Kassman, M.D., Gilbert Ledesma, M.D., Harold G McNeil, D.O., Jerry L Miller, M.D., Radman

Donald R Abrahm, M.D., Syed Sabahat Ali, M.D., Michael D Baldinger, M.D., Mark E Baxter, M.D., Benigno B Bobon, M.D., Francis X Burch, M.D., Nasim Golzar, M.D., Marvin A Heuer, M.D., Rokay Kamyar, M.D., Seth R Lewis, M.D., David Louis Limauro, M.D., Simon D Murray, M.D., Brian W Pugh, D.O., Charles Wilson Randall, M.D., J. David Schmitz, S3B30012 with:

S3B30013 with:

S3B30020 with: Ronald E Pruitt, M.D., Lee R Rocamora, M.D., Bruce E Stein, M.D., Ira E Stein, M.D., William R Stern, M.D., John A Winder, M.D. Walter Hood, M.D., Donald G Kaufman, M.D., Marc S Kaufman, M.D., Edwin Larkai, M.D., Hari N Malik, M.D., David J Morin, M.D., William S Mullican, M.D., John E Pappas, M.D., Ph.D., Sudhir K Dutta, M.D., W. Travis Ellison, M.D., Martin I Golding, M.D., William R Harlan, III, M.D., M Scott Harris, M.D., James R Herron, M.D., Robert Holmes, M.D., E Kevin Howard Ashby, M.D., Jacques R. Caldwell, M.D., Rand F Compton, M.D., Gordon T Connor, M.D., Chrystian Dallaire, M.D., FRCP, CSPQ, Ghhislain Devroede, M.D., MSc

Lawrence B Cohen, M.D., Samuel J Daniel, M.D., Matthew G Davis, M.D., Pankaj K Kashyap, M.D

S3BA3003 with:

Eugene J Burbige, M.D., Oliver D Gilliam, M.D., Michael W Gorsky, M.D., Charles D Hanshaw, M.D., Chester W Kessler, M.D.

23-Dec-1999 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial 10-Day ADR Report Initial

0159

Serial No.: 0159

Protocol: S3B30012 ADR: A0107932A

Other 1572 Change

Investigator Add

Chronology CARDS

LAM78906

Application: 23-Mar-2000 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: AI N

Document Type

Document Subtype

Serial / Supp #

63 09:47:32

IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator

Date

Communication Type

Serial No.: 0160

Protocol with Investigator(s):

Robert M Finlaw, M.D.

S3B20023 with:

Stern, M.D. David Armstrong, M.D., FRCP(C), Jacques R. Caldwell, M.D., Georges Choueri, M.D., Steven C Harnack, M.D., David G Mangels, M.D., Amit Kumar Srivastava, M.D., William R

S3B30011 with:

Enrique Carlos M. De Castro, M.D., Mark I DeBruin, D.O., R David Ferrera, M.D., Edwin B Flanagan, D.O., Marie Monique Forred, M.D., Harvey A Giller, M.D., Robert Hardi, M.D., David R Hassman, D.O., Marvin A Heuer, M.D., Thomas E Melchione, M.D., Joseph P Moore, M.D., Gayle S Moyer, M.D., Gary E Poleynard, M.D., Steven E Roberts, M.D., David J Wenzel, M.D., Douglas Young, M.D.

S3B30012 with:

Shari Anne Brazinsky, M.D., Michael S Fedotin, M.D., Zafar Sheikh, M.D., Frank A Zazueta, M.D.

S3B30013 with:

M Angeli Adamczyk, M.D., David Armstrong, M.D., FRCP(C), Charles K Bedard, M.D., Georges Choueri, M.D., Robert M Gannan, M.D., George Koval, M.D., Dale P Murphy, M.D., Frederick H Opper, M.D., Pierre Pare, M.D., Richard Warren Tobin, M.D., John A Walker, M.D.

S3BA3003 with:

Thomas McDonald, M.D., Bruce E Stein, M.D., M. Scott Touger, M.D.

21-Jan-2000

Glaxo Wellcome Correspondence

Protocol Amendment: Change in Protocol

Clinical

0162

Protocol Amendment: Change in Protocol

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

CARDS

23-Mar-2000 LAM78906 Chronology

09:47:32

Date Range: Application: ΑII N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Serial No.: 0162 Document Type Document Subtype Serial / Supp #

S3B20023 with: Protocol with Amendment(s):

S3B30006 with:

S3B30013 with:

Protocol with Report(s):

S3B20023 with: RM1999/00206/01

S3B30006 with: RM1998/00353/06

S3B30013 with:

RM1999/00195/01

31-Jan-2000 Glaxo Wellcome Correspondence

Other 1572 Change Investigator Add

Protocol Amendment: New Investigator

0163

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0163 Protocol Amendment: New Investigator

S3B20015 with: Protocol with Investigator(s):

Jay G Beckwith, M.D., E Walter Hood, M.D., Troy Alan Tyner, M.D., Richard White, M.D.

S3B20023 with:

White, M.D., Lawrence D Wruble, M.D. Rafelson, M.D., Richard I Rothstein, M.D., William B Smith, M.D., Thomas Andrew Sylwestowicz, M.D., Kevin L Tack, M.D., Volkan O Taskin, M.D., Vincent F Vacca, M.D., Richard McCluskey, M.D., Anil Minocha, M.D., Vijay Narayen, M.D., Frederick H Opper, M.D., William M Pandak, M.D., Gary E Poleynard, M.D., Ronald Scott Powell, M.D., Stephen A Harris, M.D., M Scott Harris, M.D., Paul D King, M.D., George Koval, M.D., Daniel M Kruss, M.D., Louis R Lambiase, M.D., Ben George Lazarus, D.O., S Jon Mason, M.D., Dennis C Mark Atin, FRCP(C), Brian Thomas Bock, D.O., Mark A Bonner, M.D., Fred C Fowler, M.D., Stanley B Goldberg, M.D., Marshall T Hale, M.D., Robert A Hammer, M.D., H Freeman

S3B30006 with:

Lin Chang, M.D., Robert M Finlaw, M.D., Syam P Gaddam, M.D., William H Holderman, M.D., H. Charles Miller, M.D.

'S3B30012 with:

S3B30013 with: Thaddeus M Bort, M.D., Walter E Donnelly, M.D., Harold F Grooms, M.D., Steven J Gustaveson, M.D., Joseph P Hazen, M.D., Timothy J McCarren, M.D.

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23-Mar-2000 LAM78906 Chronology 65 09:47:32

Date Range: Application: N 48487; GR68755 Tablets (alosetron hydrochloride)

Date Communication Type Document Type Document Subtype

Christopher J Lahr, M.D., F.A.C.S., Scot Michael Lewey, D.O., Mark L Lloyd, M.D., Donald E Loew, M.D., Oscar Martinez, M.D., Igor Prokopiw, M.D., Stephen A Rafelson, M.D., Amit Kumar Srivastava, M.D., Kevin L Tack, M.D., Troy Alan Tyner, M.D., Craig W Wiesenhutter, M.D. Brian Thomas Bock, D.O., John K DiBaise, M.D., Marshall T Hale, M.D., Steven C Harnack, M.D., H Freeman Harris, M.D., Vernon G.K. Hee, M.D., Spencer B Jones, M.D.,

Serial / Supp #

S3B30015 with:

S3B30019 with: Paul E Hyman, M.D., Gregory P Scagnelli, M.D., William N Sokol, Jr., M.D., Ramon Torres-Pinedo, M.D.

S3B30020 with: Paul E Hyman, M.D., Gregory P Scagnelli, M.D., William N Sokol, M.D., Ramon Torres-Pinedo, M.D.

Brian K Hudes, M.D., John D Irvin, M.D., Anne L Macek, M.D., Jorge A Prieto, M.D., Thomas G Shetter, M.D., Mark Victor Shumeyko, M.D., Stanley R Walker, M.D. Maxwell M Chait, M.D., Tawfik N Chami, M.D., Richard A Craven, M.D., Ritchard L Fishman, M.D., Michael R Gedeon, M.D., Frederick M Gessner, M.D., Jerome Howard, M.D.,

Michael F Elmore, M.D.

03-Feb-2000 Glaxo Wellcome Correspondence IND 59,496; Alosetron Hydrochloride Oral Solution Serial No.: 0164 IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Initial

0164

Protocol: S3BB3002

Serial No.: 0003

10-Day ADR Report: Initial

ADR: B0070503A

10-Feb-2000 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change Investigator Add 0165

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0165

Protocol with Investigator(s):

S3B10934 with:

Jeffrey L Blumer, M.D.

S3B20023 with:

S3B30012 with 'Ronald Ford Bursey, M.D., Donald Duerksen, M.D., FRCP(C), Carlo Fallone, M.D., CM, FRCP(C), David A Johnson, M.D., Benjamin Lasko, M.D., Elliot M Morris, M.D., William S Mullican, M.D., David Jay Schneiderman, M.D., FACS

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23-Mar-2000 Chronology

Date Range: Application: 48487; GR68755 Tablets (alosetron hydrochloride)

P Frederick Duckworth, Jr., M.D., Robert Scott Kaufmann, M.D., FACP, Radha P Narayanan, M.D., Rakesh Prasad, M.D Communication Type Document Type Document Subtype Serial / Supp #

Date

Ronald Ford Bursey, M.D., Donald Duerksen, M.D., FRCP(C), Benjamin Lasko, M.D., Joseph Reddy, M.D., Thomas Andrew Sylwestowicz, M.D.

S3B30015 with:

Scot Michael Lewey, D.O.

S3B30019 with:

Scot Michael Lewey, D.O.

S3B30020 with:

Cyrus A Badii, M.D., Gary R Bodner, M.D., Richard W Brown, M.D., Ralph L Burke, M.D., Thomas J Byer, M.D., Charles J Cattano, M.D., F.A.C.P., Peter N Christie, D.O., David H.B. Cort, M.D., David M Felig, M.D., Daniel E Gremillion, M.D., Kirk D Jacobson, M.D., Fred A Levin, M.D., Rao V Movva, M.D., Morris A Pollock, M.D., John E Poulous, M.D., Myron L Rodos, D.O., Bavikatte N Shivakumar, M.D., Richard C Siler, M.D., Leonard B Weinstock, M.D., Robert A Weiss, M.D., Felice R Zwas, M.D.

21-Feb-2000 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change Investigator Add 0166

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator

Protocol with Investigator(s)

M.D., Troy Alan Tyner, M.D., Richard A Wright, M.D. Murphy, M.D., Bennett H Plotnick, M.D., Joseph Reddy, M.D., David S Schulman, M.D., Howard I. Schwartz, M.D., Reza Shaker, M.D., Kevin L Tack, M.D., Richard Warren Tobin, Sawyer Goff, M.D., James M Gordon, M.D., M Scott Harris, M.D., Christopher J Lahr, M.D., F.A.C.S., Benjamin F Lewis, M.D., Emeran A Mayer, M.D., Peter L Moses, M.D., Dale P Matthew Acampora, M.D., Sydney Bass, M.D., Gerald Bertiger, M.D., D Eric Bolster, M.D., Alan Cockeram, M.D., FRCP(C), John K DiBaise, M.D., James E Gardiner, M.D., John

S3B30011 with:

Wilson, M.D. Steven M Adkins, M.D., David W Dozer, M.D., John D Gabriel, M.D., John F Johanson, M.D., Gilbert Ledesma, M.D., Michael J McCartney, M.D., Albert J Razzetti, M.D., Steven

S3B30012 with:

S3B30013 with: Malik N Baz, M.D.

Smith, M.D., Richard A Wright, M.D. Daniel M Kruss, M.D., Ben George Lazarus, D.O., N Martin Lunde, M.D., Emeran A Mayer, M.D., Bennett H Plotnick, M.D., Ronald Scott Powell, M.D., Reza Shaker, M.D., William B Matthew Acampora, M.D., Gary M Barton, M.D., Sydney Bass, M.D., Alan Cockeram, M.D., FRCP(C), John K Earl, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Matthew Acampora, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Carlo Fallone, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Carlo Fallone, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Carlo Fallone, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Carlo Fallone, M.D., Carlo Fallone, M.D., Carlo Fallone, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Carlo Fallone, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Carlo Fallone, M.D., C

S3B30015 with:

Michael Cosgrove, M.D., Harry A Cynamon, M.D., Lars Danielson, M.D., G Kevin Donovan, M.D., Alejandro F Flores, M.D., Jan-Ake Hammersjo, M.D., Jeffrey S Hyams, M.D., Huw Ritchie Jenkins, M.D., Eva Lindberg, M.D., Josefa Martinez, M.D., Anthony R Otley, M.D. FRCPC, Richard L Sigmon, Jr., M.D., Lars Stenhammer, Assistant Professor

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23-Mar-2000 Chronology 09:47:32

Date Range: Application: ΑII N 48487; GR68755 Tablets (alosetron hydrochloride)

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Otley, M.D. FRCPC, Richard L Sigmon, Jr., M.D., Lars Stenhammer, Assistant Professor Harry A Cynamon, M.D., Lars Danielson, M.D., G Kevin Donovan, M.D., Alejandro F Flores, M.D., Jan-Ake Hammersjo, M.D., Jeffrey S Hyams, M.D., Eva Lindberg, M.D., Anthony R Date Communication Type Document Type Document Subtype Serial / Supp #

S3B30020 with:

M.D., Sandra Tirado, M.D., Fei-Sen Yung, M.D. M.D., Kumar Mukerjee, M.D., Richard M Pavelock, M.D., Gregory J Pleasants, M.D., Alan A Rosen, M.D., Joshua Beule Shipley, M.D., Lawrence B Stein, M.D., Werner A Studer, Kaiser, M.D., Mario D Kamionkowski, M.D., Robert W Keller, M.D., Niko I Keys, M.D., Ben George Lazarus, D.O., W Park McGehee, M.D., Adrian Meyer, M.D., Stephen H. Miller, Stuart Friedman, M.D., William Lewis Gray, M.D., David M Gutman, M.D., Ruth A Hamad, M.D., Joseph Jue-Teng Hsu, M.D., John S Jackson, M.D., Thomas G Jenko, M.D., Steven C A Carron, M.D., Laura M Cho, M.D., Victor J Croglio, M.D., Mark DeFrancesco, M.D., Mark K Detweiler, M.D., David J Drewitz, M.D., Bryan N Feldman, D.O., Glenn S Freed, D.O., William Anderson, M.D., Mohammad S Anwar, M.D., Manuel E Babaian, M.D., S Murthy Badiga, M.D., Robert C Barnes, M.D., Michael D Bender, M.D., Steven A Berley, D.O., David

24-Feb-2000 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Follow-up 0167

Serial No.: 0005 10-Day ADR Report: Follow-up

Serial No.: 0167

IND 59,496; Alosetron Hydrochloride Oral Solution

ADR: A0108355A Protocol: S3B30011

25-Feb-2000 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Amendment: Other Protocol Amendment: New Protocol Research Organization Investigator Add Transfer of Obligations to Contract 0168

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Protocol

Protocol Amendment: New Investigator

Amendment: Other, Transfer of Obligations to Contract Research Organization

Serial No.: 0168

Protocol: S3B40031

Protocol with Investigator(s):

S3B40031 with:

James T. Farrell, D.O. Protocol with Report(s):

\$3B40031 with:

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23-Mar-2000 Chronology

48487; GR68755 Tablets (alosetron hydrochloride)

RM2000/00022/00 Date Communication Type Document Type Document Subtype Serial / Supp #

Comment: Kern McNeil International, Weston One, 1001 Winstead Drrive, Suite 530, Cary, NC 27513

Date Range: Application: LAM78906

01-Mar-2000 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change Investigator Add 0169

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0169

Protocol with Investigator(s)

B. Ulysses Kwang Li, M.D

E Walter Hood, M.D., Charles W Scowcroft, M.D.

S3B20023 with:

Ajit S Arora, M.D., William H Bobbitt, III, M.D., Kathleen L Collins, M.D., William Randall Cox, M.D., Paul Martin Craig, M.D., Michael J Goldstein, M.D., Stephen L Ionna, M.D., S3B30011 with: Frederick M. Braunstein, M.D., Raquel Croitoru, M.D., E Walter Hood, M.D., David G Mangels, M.D., Emeran A Mayer, M.D.

Jerry L Miller, M.D., Bryan C Pogue, M.D., Larry R Popeil, M.D., FAAFP, William N Sokol, Jr., M.D., Dale A Sundwall, M.D., FACOG, Arthur S Waldbaum, M.D.

S3B30012 with: Francis X Burch, M.D., Robert B Nett, Jr., M.D., Barry D Winston, M.D.

Frederick M. Braunstein, M.D., James M Gordon, M.D., Elliot M Morris, M.D., Mark Reichelderfer, M.D.

Bisher Abdullah, M.D., Ramalingam Arumugam, M.D., Lawrence J Hak, M.D., Joseph R.A. Ignacio, M.D., Paul J Lebovitz, M.D., Dror Wasserman, M.D.

Bisher Abdullah, M.D., Ramalingam Arumugam, M.D., Lawrence J Hak, M.D., Joseph R.A. Ignacio, M.D., Paul J Lebovitz, M.D., Dror Wasserman, M.D.

S3B30020 with:

Strzinek, Ph.D., D.O., Kosuke Tokunaga, M.D., Charles T Tweel, M.D., Katheryne A Wagner, M.D., Carl G West, M.D., Louis J Wilson, M.D., Amir Wind, M.D., Barry D Winston Trong Nguyen, M.D., Steven L Palley, M.D., Charles H Parker, Jr., M.D., James B Parsons, M.D., Anil C Patel, M.D., MBA, Tri Minh Pham, M.D., Steven L Saunders, M.D.FACP, Rajiv Shah, M.D., Suryakant M Shah, M.D., Alex Sherman, M.D., Manuel Sklar, M.D., William J Snape, Jr., M.D., Timothy J Spurling, M.D., Kenneth Robert Stringer, M.D., Robert A Medoff, M.D., FACG, Moussa Y Menasha, M.D., Moothedath A Menon, M.D., Anthony G Miccio, M.D., Peter J Molloy, M.D., Stephen J Morris, M.D., Amrit P.S. Narula, M.D., Tuan David Y Kawashiri, M.D., Jeffrey K Klingenstein, M.D., Jay A Kravitz, M.D., M.P.H., Michael Z Kurtz, D.O, P. R. Lewin, M.D., David Lin, M.D., Manish Madan, M.D., Jeffrey R David W Gothard, M.D., Mark G Griffin, M.D., Samuel I Han, M.D., Stephen K Hasley, M.D., Al N Hawks, M.D., David S Hunter, M.D., Mark Jacobs, M.D., Franklin E Kasmin, M.D., Caceres, M.D., Pundari K Chemitiganti, M.D., Gregory J Clark, M.D., Bruce C Corser, M.D., Gordon W Decker, M.D., Steven L Duckor, M.D., Jose M Duran, M.D., Ph.D., Todd D Eisner, M.D., Serhat Erzurum, M.D., Mitchell S Flaxman, M.D., Kenneth K Gheysar, M.D., Charles A Gonzalez, M.D., Paulino J Gonzalez, M.D., Glen L Gordon, M.D., FACP, FACIP, Joseph M Alcorn, M.D., Peter Arcuri, D.O., Ph.D., Jody S Berner, M.D., R. Allen Blosser, M.D., Robert R Brinson, M.D., Dennis K Buth, M.D., LeRoy J Byrd, M.D., Mauricio H

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LAM78906 23-Mar-2000 Chronology 09:47:32

Date Range: Application: ΑII N 48487; GR68755 Tablets (alosetron hydrochloride)

S3BA3003 with: Date Communication Type Document Type Document Subtype Serial / Supp #

03-Mar-2000 Glaxo Wellcome Correspondence

Protocol Amendment: Change in Protocol

Clinical

0170

Paul J Lebovitz, M.D.

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0170 Protocol Amendment: Change in Protocol

Protocol with Amendment(s):

S3B30020 with:

Protocol with Report(s):

S3B30020 with:

RC1999/00013/02

06-Mar-2000 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Other 1572 Change Investigator Add 0171

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol Amendment: New Investigator

Serial No.: 0171

Protocol with Investigator(s):

S3B20015 with:

Philip B Miner, M.D.

S3B20023 with:

Michael T Draelos, M.D.

S3B30006 with:

Charles K Bedard, M.D., Richard Fisher, M.D., Steven Krumholz, M.D., John Q Stauffer, M.D.

S3B30013 with:

Steven C Harnack, M.D., Natarajan Ravendhran, M.D., Janet S Specter, M.D., William R Stern, M.D.

S3B30020 with:

Black, M.D., Phillip L Bressman, M.D., Jack H Bumgardner, Jr., M.D., Shekhar K Challa, M.D., Brian D Clarke, M.D., Monika M Cohen, M.D., John M Cook, M.D., Tonya Davis-Spaulding, M.D., Thomas R Degregory, M.D., Atilla Ertan, M.D., Michael A Faber, M.D., Ira L Flax, M.D., Tim E Folse, M.D., Donald E Frein, M.D., Richard A Geisman, M.D., Fadi Ghanem, M.D., Richard D Gordon, M.D., David R Heiman, M.D., E Coy Irvin, Jr., M.D., Allan L Kurtz, D.O., Lyle D Kurtz, M.D., Michael J Lipson, M.D., Paul N Maton, M.D., John Abdulian, M.D., Steven J Alexander, M.D., Joseph P Ambrose, M.D., Damian H Augustyn, M.D., Dwight L Bailey, M.D., Alan R Bank, M.D., Gerald Bertiger, M.D., David J

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Regulatory Affairs

23-Mar-2000 LAM78906 Chronology

Date Range: Application: ΑI 48487; GR68755 Tablets (alosetron hydrochloride)

David K McDonald, M.D., Kalph D McKibbin, M.D., Daniel A Meline, M.D., P.C., Elliot Allen Meltzer, M.D., Bharat K Misra, M.D., Morry Moskovitz, M.D., Sam Moskovitz, M.D., Date Communication Type Document Type Document Subtype Serial / Supp #

Smith, M.D., Jonathan S Staub, M.D., John B Sturgeon, M.D., Basil S Waldbaum, M.D., Joseph L Wang, M.D., William S Watkins, M.D., John T Watson, M.D., Henry T Wittenberg, Jr., Robert A Prestiano, Jr., M.D., Jonathon D Rand, M.D., Adisesha B Reddy, M.D., Lucian C Rice, Jr., M.D., Angelo C Rizzo, D.O., Allen J Rosenbaum, M.D., Larry I Rubin, M.D., Havinder S Sahni, M.D., William B Salt, II, M.D., Jerrold Lloyd Schwartz, M.D., Balu B Shetty, M.D., H. Paul Singh, M.D., Whitney T Slade, M.D., Glenn R Slomin, D.O., Thomas B D.O., Philip C Yee, M.D., Yuen S Yee, M.D. Souheil Moussly, M.D., Mark A Nagrani, M.D., Ramalingeswara R Nimmagadda, M.D., Martin M Nosan, M.D., Raman M Patel, M.D., Crescenzo Pisano, M.D., Bernard J Powers, M.D.,

10-Mar-2000 Glaxo Wellcome Correspondence

Protocol Amendment: New Investigator

Other 1572 Change Investigator Add

0172

Protocol Amendment: New Investigator IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Protocol with Investigator(s)

Serial No.: 0172

R Walter Powell, M.D., Barbara K Zedler, M.D.

Louis R Lambiase, M.D.

S3B30015 with:

Urban Mydral, M.D., Christopher John Taylor, Professor, Michael Thomson, M.D., Pedro Uruzzuno, M.D.

S3B30019 with:

Luz Cilleruelo, M.D., Urban Mydral, M.D., Pedro Uruzzuno, M.D

S3B30020 with:

M.D., Richard M Sperling, M.D., Eliot H Zimbalist, M.D. Kallianos, M.D., Peter Shin Kay, M.D., Thomas C Kockinis, M.D., Michael J Lipson, M.D., Leslie J Nowitz, M.D., Prakash B Patel, M.D., Joseph LaRue Richter, M.D., Dallas M Shone, Crumbliss, M.D., Orin L Davidson, III, M.D., David C Duncan, M.D., Komaranahalli P Ganeshappa, M.D., Michael R Greenberg, M.D., M.B.A, Robert D Gross, M.D., John Andrew Waldo L Avello, M.D., Bruce D Beck, M.D., Samuel A Berkman, M.D., Howard L Bernie, M.D., Don R Bosse, M.D., Richard G Byrd, M.D., William D Chey, M.D., Joseph H

16-Mar-2000 Glaxo Wellcome Correspondence

Protocol Amendment: Change in Protoco

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0173

Protocol Amendment: Change in Protocol

Clinica

0173

Protocol with Amendment(s):

S3B30012 with:

LAM78906 23-Mar-2000

Regulatory Affairs CARDS

Chronology

71 09:47:32

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)

Date Range: All

Protocol with Report(s): Date Communication Type Document Type Document Subtype Serial / Supp #

21-Mar-2000 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator

0175

0174

S3B30012 with: RC1999/00003/02

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator

Serial No.: 0175

21-Mar-2000 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Initial

Serial No.: 0174
IND 59,496; Alosetron Hydrochloride Oral Solution

Serial No.: 0006

10-Day ADR Report: Initial

Protocol: S3B20023

ADR: A0114615A

22-Mar-2000 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Follow-up

0176

IND 59,496; Alosetron Hydrochloride Oral Solution

Serial No.: 0007

Serial No.: 0176

10-Day ADR Report: Follow-up

Protocol: S3B30011

ADR: A0107106A

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	Document Chronology / Due Diligence Logs for	
E	NDA 21-107	
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Chronology

10:04:33

Date Range: Application: ΑII NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

23-Mar-2000 LAM78906

24-Jun-1999 Date Glaxo Wellcome Correspondence Communication Type User Fee Document Type With Clinical Data Document Subtype Establishment Serial / Supp #

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

User Fee: With Clinical Data

29-Jun-1999 Glaxo Wellcome Correspondence User Fee Original Submission

Establishment

Patent Information

Protocol: S3B20012, S3B20013, S3B20015, S3B30004, S3B30006, S3BA1006, S3BA2002, S3BB3001, S3BB3002

GCP/92/087

C9359 with:

AS02 with: JJD/94/002 C92-087 with: GMH/92/057 C92-057 with: GCP/92/019 C92-019 with: GCP/92/006 C92-006 with: GCP/92/058 C92-058 with: AS03 with: JJD/94/001 AS01 with: Protocol with Report(s): JJD/94/003 Original Submission General Correspondence: DMF, Patent Information User Fee: Establishment NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence

Chronology CARDS

Document Type

Document Subtype

Serial / Supp #

2 10:04:33

Date Range: All

23-Mar-2000 LAM78906

Application: NDA 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

S3B201 with: S3B101 with: GPK/90/006 GPK9001 with: GMH/91/015 GHP8944 with: GHP8938 with: GMH/90/009 GHP8937 with: GHP8923 with: S3B102 with: GPK/90/008 GPK9002 with: GHP9027 with: GMH/91/002 GHP9021 with: GMH/91/007 GMH/90/012 GHP9005 with: GPK/91/005 GMH/90/004 GMH/89/024 GMH/91/025 GHP8917 with: GMH/91/051 G91-019 with: GCP/95/048 UCP/93/009 UCP/92/019 UCP/91/014 GHP9016 with: GPK/91/007 GHP9013 with: C94014 with: FNL/94/004 Date Communication Type

NN1999/00011/00 S3BA1002 with:

S3BA1001 with:

Chronology CARDS

3 10:04:33

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date Range:

23-Mar-2000 LAM78906

NN1999/00025/00 S3BA1004 with: NN1999/00032/00 Date Communication Type Document Type Document Subtype Serial / Supp #

RM1997/00819/00 S3BA2003 with: GM1997/00189/00, RM1997/00436/02

S3BA2001 with:

S3BA3001 with: RM1998/00429/00

S3BA3002 with: RM1998/00430/00

RM1998/00487/00 S3BA3003 with:

S3BB1003 with: GM1997/00307/00 S3BB1001 with:

S3BB1004 with: GM1998/00196/00

S3BB1006 with: NN1996/00003/00

GM1999/00098/00

S3BB1007 with:

S3BB1009 with: GM1997/00310/00

GM1999/00049/00

S3BB1010 with:

S3BB1011 with: PM1999/00001/00

NN1998/00003/00

S3BB2011 with:

GM1998/00275/00

S3BH01 with:

S3BH02 with: GGN/93/010

S3BH03 with: GGN/93/011

GGN/93/012 S3BH04 with:

Chronology CARDS

Application: 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

23-Mar-2000 LAM78906

GGN/93/013 GGN/94/020 S3BH05 with: Date Range: Date Communication Type

Document Type

Document Subtype

Serial / Supp #

10:04:33

FNL/94/005 S3BH08 with:

S3BH06 with:

GM1998/00287/00

S3BP12 with:

GGN/94/022

WPT/92/095, WPT/92/325, WPT/93/134, WPT/93/360, WPT/93/503, WPT/95/148 WPT/90/164, WPT/90/188, WPT/90/229, WPT/90/302, WPT/90/304, WPT/90/335, WPT/91/002, WPT/91/012, WPT/91/024, WPT/91/058, WPT/91/164, WPT/91/409, WPT/92/025 WPT/89/242, WPT/89/244, WPT/89/247, WPT/89/249, WPT/89/250, WPT/89/271, WPT/89/282, WPT/89/328, WPT/89/330, WPT/90/014, WPT/90/131, WPT/90/161, WPT/90/163, Comment: Patent No.: 5,360,900 Ex Date: 2 Feb 10 WNP/90/008, WNP/92/060, WPT/88/069, WPT/89/056, WPT/89/103, WPT/89/152, WPT/89/166, WPT/89/188, WPT/89/202, WPT/89/211, WPT/89/214, WPT/89/218, WPT/89/237, WD1998/00330/00, WD1998/00402/00, WD1999/00113/00, WGP/93/021, WNP/89/056, WNP/89/057, WNP/89/069, WNP/90/004, WNP/90/005, WNP/90/006, WNP/90/007, WNP/90/003, WNP/90/006, WNP/90/007, WNP/90/003, WNP/90/006, WNP/90/007, WNP/90/008, WNP/90/008, WNP/90/008, WNP/90/007, WNP/90/008, WNP/90/008, WNP/90/008, WNP/90/007, WNP/90/008, WWBP/92/088, WBP/92/129, WBP/93/013, WBP/93/019, WBP/93/020, WBP/93/029, WBP/94/012, WBP/94/037, WBP/95/042, WBP/95/048, WD1998/00003/00, WD1998/00191/00, WD1998/00003/00, WD1998/00191/00, WD1998/00, WD1WBP/91/017, WBP/91/041, WBP/91/044, WBP/91/045, WBP/91/046, WBP/91/047, WBP/91/098, WBP/91/099, WBP/91/105, WBP/91/108, WBP/92/011, WBP/92/021, WBP/92/037, WBP/90/041, WBP/90/052, WBP/90/055, WBP/90/056, WBP/90/057, WBP/90/062, WBP/90/063, WBP/90/069, WBP/90/073, WBP/90/097, WBP/90/099, WBP/91/002, WBP/91/008, Report: NME/94/030, SR1999/00022/00, SR1999/00023/00, SR1999/00029/00, WBP/89/046, WBP/89/060, WBP/89/062, WBP/89/071, WBP/89/097, WBP/89/100, WBP/89/101, WBP/89/071, WBP/89/097, WBP/89/100, WBP/89/101, WBP/89/071, WBP/89/097, WBP/89/100, WBP/89/101, WBP/89/071, WBP/89/071, WBP/89/071, WBP/89/100, WBP/89/101, WBP/89/071, WBP/89/071, WBP/89/071, WBP/89/071, WBP/89/100, WBP/89/101, WBP/89/071, WBP/89/071, WBP/89/100, WBP/89/101, WBP/89/071, WBP/89/071, WBP/89/071, WBP/89/071, WBP/89/101, WBP/89/071, WBP/8

29-Jun-1999 Glaxo Wellcome Correspondence

Response to FDA Request/Comment

Clinical

Response to FDA Request/Comment: Clinical NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Protocol with Report(s): Protocol: S3BA1006, S3BA2001, S3BA2002, S3BA3001, S3BA3002, S3BA3003, S3BB1002, S3BP12

AS01 with:

JJD/94/001

GCP/92/006 C92-006 with:

GCP/92/019 C92-019 with:

C92-057 with

C9359 with: GCP/92/057

- FNL/94/004 C94014 with

Chronology **CARDS**

5 10:04:33

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date Range: All

23-Mar-2000 LAM78906

- GM1998/00275/00 S3BH01 with:

S3BB2011 with: GM1999/00049/00 S3BB1009 with:

S3BB1007 with: GM1997/00310/00

GM1999/00098/00 S3BB1006 with: GM1998/00196/00 S3BB1003 with: GM1997/00307/00 S3BB1001 with: NN1998/00093/00

S3BA1001 with: UCP/91/014 S3B101 with: GMH/91/015 GHP9027 with:

RM1998/00819/00 S3BA2003 with: NN1999/00032/00 S3BA1002 with: GMH/91/007

GHP9016 with: GMH/90/012 GHP9005 with: GMH/90/004 GHP8938 with: GMH/90/009 GHP8937 with: GMH/89/024 GHP8923 with: GMH/91/025 GHP8917 with:

Date Com	Communication Type	Document Type	Document Subtype	Serial / Supp #
GCP/95/048				
G91-019 with:				
GMH/91/051				

LAM78906 Chronology CARDS

GM1998/00287/00 GGN/94/020 GGN/93/013 S3BH08 with: S3BH06 with: S3BH05 with: S3BH04 with: GGN/93/012 S3BH03 with: GGN/93/011 S3BH02 with: GGN/93/010 FNL/94/005 Date Range: Application: 23-Mar-2000 09-Jul-1999 06-Jul-1999 09-Jul-1999 13-Jul-1999 Date All NDA Glaxo Wellcome Telephone Conversation Food and Drug Administration Telephone General Teleconference: Other, Safety NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Food and Drug Administration Correspondence Glaxo Wellcome Telephone Conversation Acknowledgement: Receipt of NDA NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Other - NDA Administrative Issues NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Communication Type 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference General Teleconference General Teleconference Acknowledgement Document Type Other Safety Other Status Update 060-Day Review Extension Document Subtype Serial / Supp # 6 10:04:33

Chronology CARDS

Application: NDA All 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Date Range:

Date

23-Mar-2000 LAM78906

Communication Type Document Type

Document Subtype

Serial / Supp #

NDA 21-036; RELENZA® (zanamivir for inhalation)

General Teleconference: Status Update

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

General Teleconference: Status Update

NDA 21-077; ADVAIR™ DISKUS® (salmeterol/fluticasone propionate inhalation powder) 100 mcg, 250 mcg and 500 mcg

General Teleconference: Other, Status Update

27-Jul-1999 Food and Drug Administration Telephone NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference Conversation General Teleconference Status Update

02-Aug-1999 Glaxo Wellcome Telephone Conversation

Response to FDA Request/Comment

BA/BE Clinical Advisory Committee Meeting

CMC

Response to FDA Request/Comment: , BA/BE, Clinical, CMC, Advisory Committee Meeting NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

05-Aug-1999 Glaxo Wellcome FAX/E-mail

Response to FDA Request/Comment

Other BA/BE

Response to FDA Request NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

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LAM78906 23-Mar-2000 Chronology

Application: NDA
Date Range: All 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date	Date Communication Type	Document Type Comment/Information Request	Document Subtype
05-Aug-1999	05-Aug-1999 Food and Drug Administration Telephone	Comment/Information Request	
	Conversation		

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: BA/BE, Clinical, CMC, DMF, Electronic Format, Other, Statistical

06-Aug-1999
06-Aug-1999 Food and Drug Administration Telephone Conversation
Comment/Information Request
CMC

-Aug-1999 Glaxo Wellcome FAX/	
E-mail Response to FDA Request/Comment	
Other	

Protocol: S3BA3001, S3BA3002

Response to FDA Request/Comment: Other - SAS Dataset Question

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Clinical	Comment information Kequest	09-Aug-1999 Food and Drug Administration Telephone	Aug-1999
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NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Statistical

Protocol: S3BB1004

. Commitment: Amendment to correct PK Summary (food effects study S3BB1004 Commitment Responsibility: K Kock/ M Baumgartner

LAM78906 23-Mar-2000 Chronology CARDS

Application: NDA 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Date Range: All

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Comment/Information Request

Electronic Format

Serial / Supp #

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NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Electronic Format

09-Aug-1999

Food and Drug Administration Telephone

Conversation

Protocol: S3BA3001, S3BA3002

Commitment: Amend the NDA to include the missing pages Commitment Responsibility: M Baumgartner

Commitment Due Date: 13-Aug-1999

10-Aug-1999	
Glaxo Wellcome Correspondence	
Response to FDA Request/Comment	
Clinical	
	ig-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical

Comment: Electronic CRF's

	10-Aug-1999	
Conversation	0-Aug-1999 Food and Drug Administration Telephone	
	Comment/Information Request	
	Electronic Format	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Electronic Format

Protocol: S3BA3001, S3BA3002

	11-Aug-1999
	11-Aug-1999 Glaxo Wellcome Telephone Conversation
	General Teleconference
CMC Meeting Request Other	Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, CMC, Meeting Request, Other

- Protocol: S3BA3001, S3BA3002

Commitment: Provide location within the application of C of As

23-Mar-2000 LAM78906

Regulatory Affairs CARDS

Chronology

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Application: 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date Range:

Date Communication Type Document Type	Document Subtype	Serial / Supp #
Commitment Responsibility: M Baumgartner		
Commitment Due Date: 12-Aug-1999		

11-Aug-1999 Food and Drug Administration Telephone Conversation Comment/Information Request

Statistical

Comment/Information Request: Statistical Reviewer Questions Regarding Datasets NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

11-Aug-1999 Food and Drug Administration FAX/E-mail Comment/Information Request Clinical

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Comment/Information Request: Clinical

13-Aug-1999 Glaxo Wellcome Telephone Conversation Response to FDA Request/Comment CMC

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment: CMC

17-Aug-1999 Food and Drug Administration Telephone Conversation

Comment/Information Request

CMC Clinical

Nonclinical

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Comment/Information Request: Clinical, CMC, Nonclinical

18-Aug-1999 Glaxo Wellcome Telephone Conversation

General Teleconference

Nonclinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Nonclinical: Datasets for oncogenicity studies

Application: Date Range: 23-Mar-2000 LAM78906 All NDA 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Chronology **CARDS** 11 10:04:33

Commitment: Submit desk copies of NDA volumes 1.10 through 1.15 and 1.24 through 1.29

Date Communication Type

Document Type

Document Subtype

Serial / Supp #

Commitment Responsibility: M Baumgartner

19-Aug-1999 Glaxo Wellcome Telephone Conversation General Teleconference

Other

Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets
General Teleconference: Other: Pharm/Tox (datasets for oncogenicity studies)

19-Aug-1999 Food and Drug Administration Telephone Conversation Comment/Information Request DMF Electronic Format Clinical

General Teleconference

Meeting Request

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets
Comment/Information Request: Clinical, DMF, Electronic Format, Safety

General Teleconference: Meeting Request

Protocol: S3BA2001, S3BA3003, S3BP12

20-Aug-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical

Protocol: S3BA2001, S3BP12

23-Aug-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment Statistical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Statistical

- Protocol: S3BA3001, S3BA3002

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23-Mar-2000 Chronology

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Application: Date Range: NDA

LAM78906

21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Date Food and Drug Administration FAX/E-mail Communication Type General Memorandum Document Type Status Update Document Subtype Serial / Supp #

General Memorandum: Status Update NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

23-Aug-1999 Glaxo Wellcome FAX/E-mail Response to FDA Request/Comment Statistical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Statistical

23-Aug-1999 NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Food and Drug Administration FAX/E-mail Comment/Information Request Statistical

Comment/Information Request: Statistical

23-Aug-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment Other BA/BE

Response to FDA Request/Comment NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

24-Aug-1999

Glaxo Wellcome Correspondence

General Correspondence

Meeting Request

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: Meeting Request

24-Aug-1999 Glaxo Wellcome FAX/E-mail

General Memorandum

Meeting Request

Application: 23-Mar-2000 LAM78906 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Chronology CARDS 10:04:33

Date Range: Date AII A Communication Type Document Type

Document Subtype

Serial / Supp #

General Memorandum: Meeting Request

NDA 21-107; LOTRONEX^{IM} (Alosetron Hydrochloride) Tablets

24-Aug-1999 Food and Drug Administration Telephone Conversation General Teleconference Status Update Meeting Agenda or Details

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Meeting Agenda or Details, Other, Status Update

24-Aug-1999 Glaxo Wellcome FAX/E-mail NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Statistical Response to FDA Request/Comment Statistical

25-Aug-1999 Glaxo Wellcome Correspondence Amendment to Pending Application Nonclinical

Report: D22693, DGRP1015, G22691, SR1999/00073/00

Amendment to Pending Application: Nonclinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Food and Drug Administration Telephone Conversation Comment/Information Request Safety Nonclinical Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Cardiac Safety Information

Protocol: S3B10932

- Commitment: Timeline evaluation for the deliverables described above. Commitment Responsibility: M Baumgartner

CARDS

23-Mar-2000 LAM78906 Chronology 14 10:04:33

Date Range: All Application: 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Date Communication
on Type
Document Type
Document Subtype
Serial / Supp #

Comment/Information Request

Other

Comment/Information Request: Other NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets 25-Aug-1999

Food and Drug Administration Telephone

Conversation

25-Aug-1999 Glaxo Wellcome FAX/E-mail NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Memorandum Nonclinical

General Memorandum: Nonclinical

	Conversation	26-Aug-1999 Food and Drug Administration Telephone Comm	Comment: Copy of BIMO cover letter and TOC.	 Response to FDA Request/Comment: Other: DSI Information	NDA 21-107; LÓTRONEX TM (Alosetron Hydrochloride) Tablets	26-Aug-1999 Glaxo Wellcome FAX/E-mail Respo
		Comment/Information Request		ion	Tablets	Response to FDA Request/Comment
CMC	Clinical	BA/BE				Other

Comment/Information Request: BA/BE, Clinical, CMC NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

27-Aug-1999 Glaxo Wellcome Correspondence

Response to FDA Request/Comment

Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical

Protocol: S3BA3003

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LAM78906 23-Mar-2000 Chronology

Application: NDA
Date Range: All 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

30-Aug-1999	Date
30-Aug-1999 Glaxo Wellcome Correspondence	Communication Type
Response to FDA Request/Comment	Document Type
Nonclinical Other	Document Subtype
	Serial / Supp #

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment: Nonclinical

					30-Aug-1999
NDA 21 107: I OTDONIEVTM (Alegatean Budrockleride) Tobleto					30-Aug-1999 Glaxo Wellcome Telephone Conversation
ochlorido) Tobleto					General Teleconference
	Request Status Update	Labeling	Efficacy	CMC	Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Request Status Update

	31-Aug-1999	
Conversation	Food and Drug Administration Telephone	
	Comment/Information Request	
Other	Nonclinical	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Correspondence: CMC, DMF

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Conversation	Food and Drug Administration Telephone	
	General Teleconference	
Other	Meeting Agenda or Details	

LAM78906 23-Mar-2000

Regulatory Affairs CARDS Chronology

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Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date Range: All

Date Communication Type Document Type Status Update Document Subtype Serial / Supp #

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

General Teleconference: Request Replacement for CRF PDF File; Status Update on Meeting Request and Question Responses

02-Sep-1999 Glaxo Wellcome Correspondence NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment Other Clinical

Comment: Replacement .pdf formatted CRF tape.

Response to FDA Request/Comment: Clinical, Other

03-Sep-1999 Glaxo Wellcome Correspondence Amendment to Pending Application Nonclinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Amendment to Pending Application: Nonclinical

Report: WD1999/00381/00

07-Sep-1999 Food and Drug Administration Telephone Conversation Comment/Information Request Other Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Other: DSI Request

Protocol with Investigator(s):

S3BA3001 with:

Lin Chang, M.D., Oscar Oandasan, M.D., Michael Safdi, M.D.

S3BA3002 with:

Scott D Bleser, D.O., Rokay Kamyar, M.D., James R Wagner, M.D.

08-Sep-1999 Glaxo Wellcome Telephone Conversation General Teleconference Other Nonclinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

23-Mar-2000 LAM78906 Chronology CARDS

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Application: AII A 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date Range:

Date Communication Type General Teleconference: Other: DSI Request Document Type Document Subtype Serial / Supp #

Protocol with Investigator(s):

S3BA3001 with:

Lin Chang, M.D., Oscar Oandasan, M.D., Michael Safdi, M.D.

S3BA3002 with:

Scott D Bleser, D.O., Rokay Kamyar, M.D., James R Wagner, M.D.

08-Sep-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Materials Requested for DSI Audits of Clinical Sites

Response to FDA Request/Comment: Clinical, Other (DSI Request) NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets 09-Sep-1999

Glaxo Wellcome FAX/E-mail

Response to FDA Request/Comment

Clinical

Protocol: S3BA2001, S3BA3001, S3BA3002, S3BP12

10-Sep-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment CMC BA/BE

Response to FDA Request/Comment: BA/BE, CMC NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Report: UCP/92/026

10-Sep-1999 Food and Drug Administration Telephone Comment/Information Request Nonclinical Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Nonclinical

Protocol: S3BA2001, S3BA3001, S3BA3002, S3BP12

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23-Mar-2000 LAM78906 Chronology 18 10:04:33

Application: Date Range: ΑI NDA 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Comment of the second s	Clinical	Comment/Information Request	10-Sep-1999 Food and Drug Administration Telephone	10-Sep-1999
Serial / Supp #	Document Subtype	Document Type	Communication Type	Date

Other

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Comment/Information Request: Clinical

Conversation

Protocol: S3BA3001

Commitment: Desk copy of 1.189

Commitment Responsibility: A Calisto

Commitment Due Date: 10-Sep-1999

13-Sep-1999 Glaxo Wellcome Correspondence NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical Response to FDA Request/Comment Clinical

Protocol: GHP8923, GHP8938, GHP9005, GHP9013, GPK9001, S3B101, S3B102, S3BA1001

14-Sep-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment Clinical

Protocol: S3BA3001, S3BA3002

Response to FDA Request/Comment: Clinical

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

14-Sep-1999

Glaxo Wellcome Telephone Conversation

General Teleconference

Meeting Agenda or Details

Advisory Committee Meeting

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Request Status Update NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting Request Status Undate	14-Sep-1999	14-Sep-1999 Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting Request Status Undate				Request Status Update
Ceneral Clescon and Soft Committee Vicentia Action Committee Commi		NDA 21-107; LOTRONEX TM (Alosetron Hydr	ochloride) Tablets	

LAM78906

23-Mar-2000

Regulatory Affairs Chronology CARDS

19 10:04:33

Date Range: Application: NDA All 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Date Communication Type General Teleconference: Advisory Committee Meeting, Meeting Agenda or Details Document Type Document Subtype Serial / Supp #

14-Sep-1999 Food and Drug Administration Telephone Conversation

General Teleconference

Nonclinical Status Update Meeting Agenda or Details

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Meeting Agenda or Details, Status Update

Comment/Information Request: Nonclinical

14-Sep-1999 Glaxo Wellcome Correspondence

Response to FDA Request/Comment

Clinical

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment: Clinical

Protocol: S3BA2001, S3BA3001, S3BA3002, S3BP12

15-Sep-1999 Glaxo Wellcome FAX/E-mail

Response to FDA Request/Comment

BA/BE

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment: BA/BE

15-Sep-1999 Glaxo Wellcome Correspondence

Response to FDA Request/Comment

Clinical

Response to FDA Request/Comment: Clinical NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Protocol: S3BA2001, S3BA3001, S3BA3002

S3B10932 with: Protocol with Report(s):

NN1999/00059/00

23-Mar-2000 LAM78906 **Regulatory Affairs** Chronology **CARDS** 20 10:04:33

Date Range: Application: ΑII NDA 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

15-Sep-1999	Date	
15-Sep-1999 Food and Drug Administration Telephone Conversation	Communication Type	
Comment/Information Request	Document Type	
Clinical	Document Subtype	
	Serial / Supp #	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Comment/Information Request: Clinical

Commitment: Submit requested records on patients Protocol: S3BA2001, S3BA3001, S3BA3002

Commitment Responsibility: M Baumgartner 17-Sep-1999 Glaxo Wellcome Correspondence Amendment to Pending Application Nonclinical

Amendment to Pending Application: Nonclinical NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Nonclinical

Report: WD1999/00383/00, WD1999/00412/00

20-Sep-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment Clinical

Response to FDA Request/Comment: Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Protocol: S3BA3002

20-Sep-1999 Glaxo Wellcome Telephone Conversation General Teleconference Advisory Committee Meeting

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting

21-Sep-1999 Glaxo Wellcome Correspondence

Response to FDA Request/Comment

Response to FDA Request/Comment: BA/BE NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Correction to Previously Submitted Information: BA/BE

BA/BE

LAM78906 23-Mar-2000

Regulatory Affairs Chronology CARDS

21 10:04:33

Application: NDA
Date Range: All

21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

		ochloride) Tablets	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Correspondence: CMC Field Copy	
	CMC Field Copy	General Correspondence	Glaxo Wellcome Correspondence	22-Sep-1999
			Concine Actividition Ciric	
		ochloride) Tablets	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets	
	CMC	General Teleconference	Glaxo Wellcome Telephone Conversation	22-Sep-1999
		chloride) Tablets eling	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Amendment to Pending Application: CMC, Labeling	
	CMC Labeling	Amendment to Pending Application	Glaxo Wellcome Correspondence	22-Sep-1999
		ochloride) Tablets go	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Request for Comments on Proposed Product Logo	
	Advertising/Promotion	General Correspondence	Glaxo Wellcome Correspondence	21-Sep-1999
			Protocol: S3B10932, S3BA3001, S3BA3003	Protocol: S3B10
		ochloride) Tablets Meeting details, submission status	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Meeting details, submission status	
	Clinical Other	Comment/Information Request	Food and Drug Administration Telephone Conversation	21-Sep-1999
Serial / Supp #	Document Subtype	Document Type	Communication Type	Date

CARDS

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23-Mar-2000 LAM78906 Chronology

Application: Date Range: All 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

	Nonclinical	Response to FDA Request/Comment	23-Sep-1999 Glaxo Wellcome FAX/E-mail	23-Sep-1999
Serial / Supp #	Document Subtype	Document Type	Date Communication Type	Date

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment: Nonclinical

	23-Sep-1999
NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets	23-Sep-1999 Food and Drug Administration Telephone Conversation
ochloride) Tablets	Comment/Information Request
	Clinical Nonclinical Other

24-Sep-1999 Glaxo W	
Glaxo Wellcome Correspondence	
120-Day Safety Update	
Safety	

Comment/Information Request: Clinical, Nonclinical, Other

90-Day Safety Update NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

RM1999/00344/00 S3BA3003 with: Protocol with Report(s):

	27-Sep-1999
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Nonclinical	27-Sep-1999 Glaxo Wellcome Telephone Conversation
rochloride) Tablets cal	Response to FDA Request/Comment
	Nonclinical

28-Sep-1999

Glaxo Wellcome FAX/E-mail

Response to FDA Request/Comment

Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment: Clinical

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Application: NDA
Date Range: All 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

	Meeting Agenda or Details	General Memorandum	29-Sep-1999 Food and Drug Administration FAX/E-mail	29-Sep-1
Serial/Supp#	Document Subtype	Document Type	Date Communication Type Totocol: N3BA3001, N3BA3002	Protocol: S

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Agenda or Details

	29-Sep-1999	
Conversation	29-Sep-1999 Food and Drug Administration Telephone	
	General Teleconference	
Other	Meeting Agenda or Details	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Meeting Agenda or Details, Other

	30-Sep-1999
NDA 21-107: I OTRONEXIM (Alosetron Hydrochloride) Tahl	30-Sep-1999 Glaxo Wellcome Correspondence
trochloride) Tahlets	General Correspondence
	Meeting Agenda or Details

01-Oct-1999	
01-Oct-1999 Food and Drug Administration FAX/E-mail	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Correspondence: Meeting Details
General Memorandum	nloride) Tablets
Advisory Committee Meeting Meeting Agenda or Details	

	01-Oct-1999			01-Oct-1999
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Memorandum: Advisory Committee Meeting	01-Oct-1999 Food and Drug Administration FAX/E-mail	-	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Memorandum: Advisory Committee Meeting	01-Oct-1999 Food and Drug Administration FAX/E-mail
chloride) Tablets eting	General Memorandum		chloride) Tablets eting	General Memorandum
	Advisory Committee Meeting			Advisory Committee Meeting Meeting Agenda or Details

LAM78906 23-Mar-2000

Regulatory Affairs

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Application: NDA
Date Range: All 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
05-Oct-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Meeting Agenda or Details	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Agenda or Details	hloride) Tablets ls		
05-Oct-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Efficacy Meeting Agenda or Details Safety	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Meeting Agenda or Details	hloride) Tablets iils		
06-Oct-1999	Glaxo Wellcome Trip Report	Туре	090-Day Conference	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Type: 090-Day Conference	hloride) Tablets		
12-Oct-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting	hloride) Tablets seting		
13-Oct-1999	Food and Drug Administration FAX/E-mail	Comment/Information Request	Clinical Efficacy Labeling	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Other Safety

23-Mar-2000 LAM78906 Chronology CARDS 25 10:04:33

Date Range: Application: Date NDA All Communication Type 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Document Type

Protocol: S3BA3001, S3BA3002

Comment/Information Request: Other

13-Oct-1999 Food and Drug Administration Telephone Conversation Comment/Information Request

Statistical

Document Subtype

Serial / Supp #

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Comment/Information Request: Statistical

Protocol: S3BA3001, S3BA3002

14-Oct-1999 Food and Drug Administration Telephone Conversation Comment/Information Request Statistical Electronic Format Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Review of Meeting Summary

Protocol: S3BA2001, S3BA3001, S3BA3002, S3BA3003, S3BP12

15-Oct-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical

Protocol: S3BA2001, S3BA3001, S3BA3002, S3BA3003, S3BP12

15-Oct-1999 Glaxo Wellcome FAX/E-mail Response to FDA Request/Comment Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical

Protocol: S3BA2001, S3BA3001, S3BA3002

21-Oct-1999 Food and Drug Administration FAX/E-mail General Memorandum Other

Application: 23-Mar-2000 LAM78906 All NDA 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Chronology CARDS 26 10:04:33

Date Range: Date Communication Type Document Type Document Subtype

Serial / Supp #

General Memorandum: Critical Data Format

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

21-Oct-1999 Glaxo Wellcome Telephone Conversation General Teleconference Safety Other Labeling Statistical

General Teleconference: Other: Status update NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

22-Oct-1999 Food and Drug Administration FAX/E-mail Comment/Information Request CMC

Comment/Information Request: CMC

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

22-Oct-1999 Food and Drug Administration Telephone NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Conversation General Teleconference Status Update

General Teleconference: Status Update

22-Oct-1999 Food and Drug Administration Correspondence Comment/Information Request CMC

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Comment/Information Request: CMC

25-Oct-1999

Glaxo Wellcome Correspondence

Response to FDA Request/Comment

Clinical

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23-Mar-2000 LAM78906 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Chronology 27 10:04:33

Application: NDA
Date Range: All

				Date	
				Communication Type	
General Correspondence				Document Type	
Meeting Request	Statistical	Nonclinical	Labeling	Document Subtype	
				Serial / Supp #	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment
Summary of Meeting Discussion Topics and Outcomes

Revised Draft Labeling
Request for Teleconference

Protocol: S3BA2001, S3BA3001, S3BA3002, S3BA3003, S3BP12

	25-Oct-1999
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Advisory Committee Preparation	25-Oct-1999 Food and Drug Administration Telephone Conversation
chloride) Tablets Advisory Committee Preparations	Comment/Information Request
	Clinical Other

	26-Oct-1999 Food and Drug Administration FAX/E-mail	
	Comment/Information Request	
Other	CMC	

	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: CMC, Other	chloride) Tablets		
26-Oct-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Other	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Memorandum: Other	chloride) Tablets		
26-Oct-1999	26-Oct-1999 Food and Drug Administration Telephone	Comment/Information Request	Clinical	Constitutional
	Conversation		Other	

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Application: Date Range: All NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

23-Mar-2000 LAM78906

Date Communication Type Document Type Document Subtype Serial / Supp #

Comment/Information Request: Clinical NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

27-Oct-1999 Glaxo Wellcome Correspondence Response to FDA Request/Comment Clinical

Response to FDA Request/Comment: Clinical NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Protocol: S3BA3001, S3BA3002, S3BA3003

27-Oct-1999 Food and Drug Administration Telephone Conversation Comment/Information Request Other CMC

Comment/Information Request: CMC, Other: Status Update NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

27-Oct-1999 Glaxo Wellcome FAX/E-mail Response to FDA Request/Comment **Advisory Committee Meeting**

Response to FDA Request/Comment: Advisory Committee Meeting NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

27-Oct-1999 Food and Drug Administration Telephone Conversation General Teleconference **Advisory Committee Meeting**

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Information

27-Oct-1999 Glaxo Wellcome FAX/E-mail

Response to FDA Request/Comment

Advisory Committee Meeting

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Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Date Range: All

LAM78906 23-Mar-2000

NDA 21-107; LOTRONEX ^{IM} (Alosetron Hydrochloriding Response to FDA Request/Comment: Advisory Commit	Date Communication Type
setron Hydrochloride) Tablets nt: Advisory Committee Meeting	Document Type
	Document Subtype
	Serial / Supp #

28-Oct-1999		28-Oct-1999
28-Oct-1999 Glaxo Wellcome Correspondence	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Correspondence Advisory Committee Meeting Briefing Document	28-Oct-1999 Glaxo Wellcome Correspondence
General Correspondence	Hydrochloride) Tablets cument	General Correspondence
Advisory Committee Meeting		Advisory Committee Meeting Meeting Agenda or Details

28-Oct-1999	28-Oct-1999 Glaxo Wellcome Correspondence	General Correspondence	Advisory Committee Meeting	
	NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets	ochloride) Tablets		
	General Correspondence: Advisory Confinities Meeting Difering Document	Meeting Diverting Document		
28-Oct-1999	28-Oct-1999 Food and Drug Administration Telephone Conversation	Comment/Information Request	Statistical	

	28-Oct-1999			28-Oct-1999
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Advertising/Promotion	28-Oct-1999 Food and Drug Administration Correspondence	_	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Statistical	28-Oct-1999 Food and Drug Administration Telephone Conversation
chloride) Tablets notion	Comment/Information Request		chloride) Tablets	Comment/Information Request
	Advertising/Promotion			Statistical

3	MACMIS: 8307			
.	9-Oct-1999	29-Oct-1999 Glaxo Wellcome Correspondence	General Correspondence	Clinical
				Other

LAM78906 23-Mar-2000

Regulatory Affairs

Chronology **CARDS** 30 10:04:33

Date Range: Application: 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

t Type Document Subtype	munication Type Document 1
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General Correspondence: PROPOSED PEDIATRIC STUDY REQUEST NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Protocol: S3B10903, S3B10934, S3B30015, S3B30016

02-Nov-1999
Glaxo Wellcome Correspondence
Response to FDA Request/Comment
CMC

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: CMC

General Correspondence: CMC Field Copy	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets
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02-Nov-1999

Glaxo Wellcome Correspondence

General Correspondence

CMC Field Copy

03-Nov-1999	
Glaxo Wellcome Telephone Conversation	
General Teleconference	
Advisory Committee Meeting	

NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting	റ്റ	Z
07; LOTRONEX™ (Alosetron Hydrochloride) Tablets ≥leconference: Advisory Committee Meeting	eneral Te	DA 21-1
RONEX TM (Alosetron Hydrochloride) Tablets ence: Advisory Committee Meeting	eleconfer	07; LOT
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drochloride) Tablets Re Meeting) Ommitte	etron Hy
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	04-Nov-1999
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Advisory Committee Meeting General Memorandum: Meeting Agenda or Details	04-Nov-1999 Glaxo Wellcome FAX/E-mail
ochloride) Tablets Committee Meeting ails	Response to FDA Request/Comment General Memorandum
	Advisory Committee Meeting Meeting Agenda or Details

04-Nov-1999	
Glaxo 1	
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Telephone	
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LAM78906 23-Mar-2000 Chronology

Application: NDA
Date Range: All 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

	Date	
	Communication Type	
	Document Type	
Labeling Meeting Agenda or Details	Document Subtype	
	Serial / Supp #	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

General Teleconference: Advisory Committee Meeting, Clinical, Labeling, Meeting Agenda or Details, Meeting Request, Request Status Update

Request Status Update Meeting Request

05-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Request Status Update	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Other: DSI	ochloride) Tablets		
05 31 1000	Class Wellows EAVE well	Gazzal Managardum	Advisor: Committee Meeting	-
05-Nov-1999	05-Nov-1999 Glaxo Wellcome FAX/E-mail	General Memorandum	Advisory Committee Meeting Meeting Agenda or Details	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Memorandum: Advisory Committee Meeting	ochloride) Tablets leeting		

05-Nov-1999		05-Nov-1999
05-Nov-1999 Glaxo Wellcome FAX/E-mail	 NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting, CMC	Glaxo Wellcome Telephone Conversation
General Memorandum	ochloride) Tablets Aeeting, CMC	General Teleconference
Advisory Committee Meeting Meeting Agenda or Details		Advisory Committee Meeting CMC

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Memorandum: Advisory Committee Meeting, Meeting Agenda or Details

LAM78906 23-Mar-2000 Regulatory Affairs CARDS Chronology

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Application: Date Range:	NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets All	drochloride) Tablets		
Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
09-Nov-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Other	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Memorandum: Other	hloride) Tablets		
09-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting CMC Efficacy Meeting Agenda or Details Request Status Update	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting, Request Status Update	hloride) Tablets æting, Request Status Update		
10-Nov-1999	Glaxo Wellcome Correspondence	General Correspondence	Other	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Correspondence: Request for Partial Waiver and Deferral of Pediatric Studies	hloride) Tablets ver and Deferral of Pediatric Studies		
Protocol: S3B10	Protocol: S3B10903, S3B10934, S3B30015, S3B30016, S3B30018, S3B30019	S3B30019		
10-Nov-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Meeting Agenda or Details	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Agenda or Details	hloride) Tablets s		
10-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting Request Status Update	

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23-Mar-2000 LAM78906 Chronology 33 10:04:33

Application: NDA
Date Range: All 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Dat	Date Communication Type	Document Type	Document Subtype	Serial / Sup
	NDA 21-107; LOTRONEXIM (NDA 21-107; LOTRONEX ^{1M} (Alosetron Hydrochloride) Tablets		
	Canaral Teleconference: Advice	General Teleconference: Advisory Committee Meeting Request Status Undate		

10-Nov-1999 Food and Drug Administration FAX/E-mail General Memorandum Meeting Agenda or Details

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Agenda or Details

10-Nov-1999 Glaxo Wellcome Telephone Conversation General Teleconference: Advisory Committee Meeting NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference Meeting Agenda or Details **Advisory Committee Meeting**

12-Nov-1999 Glaxo Wellcome FAX/E-mail General Memorandum Clinical

General Memorandum: Clinical NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Protocol: S3B30011

12-Nov-1999 Glaxo Wellcome FAX/E-mail General Memorandum Clinical

General Memorandum: Clinical NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Protocol: S3B30011

CMC		Conversation	
Clinical	Comment/Information Request	12-Nov-1999 Food and Drug Administration Telephone	12-Nov-1999

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LAM78906 23-Mar-2000 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Chronology 34 10:04:33

Application: NDA
Date Range: All

מ	Date Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochl	setron Hydrochloride) Tablets		
	Comment/Information Request: Clinical, Safety	inical, Safety		

12-Nov-1999 Glaxo Wellcome Correspondence General Correspondence Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Correspondence: Clinical

Protocol: S3B30011

	15-Nov-1999
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Advisory Committee Meeting	15-Nov-1999 Glaxo Wellcome Correspondence
drochloride) Tablets ry Committee Meeting	Response to FDA Request/Comment
	Advisory Committee Meeting

	ochloride) Tahlets	NDA 21-107: I OTRONEXTM (Alosetron Hydrochloride) Tablets	
Other		Conversation	
Clinical	Comment/Information Request	15-Nov-1999 Food and Drug Administration Telephone	15-Nov-1999

Meeting Agenda or Details	General Memorandum	15-Nov-1999 Food and Drug Administration FAX/E-mail	15-Nov-1999
	chloride) Tablets Advisory Committee Plans	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Advisory Committee Plans	
Culci		COTIACTORITION	

Protocol: S3BA3001, S3BA3002

General Memorandum: Meeting Agenda or Details

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

ı	15-Nov-1999	15-Nov-1999 Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Advisory Committee Meeting	
• •		NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets	lydrochloride) Tablets		

Response to FDA Request/Comment: Advisory Committee Meeting

LAM78906

23-Mar-2000

Regulatory Affairs

Chronology CARDS

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Application: 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Protocol: S3B30011, S3BA2001, S3BA3002 Date Range: 19-Nov-1999 19-Nov-1999 18-Nov-1999 19-Nov-1999 18-Nov-1999 Date Glaxo Wellcome Trip Report Glaxo Wellcome Correspondence NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Conversation Food and Drug Administration Telephone Glaxo Wellcome FAX/E-mail Comment/Information Request: Clinical, Safety NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Food and Drug Administration Telephone Amendment to Pending Application: Clinical Response to FDA Request/Comment: Pathology Results NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Communication Type Conversation Topic Comment/Information Request Amendment to Pending Application Comment/Information Request Response to FDA Request/Comment Document Type Safety Safety Other Labeling Clinical Other Clinica Clinical Clinica Document Subtype Serial / Supp #

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

CARDS

23-Mar-2000 LAM78906 NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Chronology 10:04:33

Application: Date Range: Date ΑII Communication Type Document Type

Document Subtype

Serial / Supp #

Topic: Clinical, Labeling, Safety

23-Nov-1999 Food and Drug Administration Telephone Conversation Comment/Information Request Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Protocol: S3BA3001, S3BA3002

Comment/Information Request: Clinical

23-Nov-1999 Glaxo Wellcome Telephone Conversation General Teleconference Clinical

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

General Teleconference: Clinical

Commitment: Correct the administrative record (information previous submitted Oct 25, 1999)

Commitment Responsibility: M Baumgartner

23-Nov-1999 NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Conversation Food and Drug Administration Telephone Comment/Information Request

Clinical

Comment/Information Request: Clinical, Other: Status update

Response to FDA Request/Comment: Clinical NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets 29-Nov-1999

Glaxo Wellcome FAX/E-mail

Response to FDA Request/Comment

Clinical

S3BA3003 with: Protocol with Report(s):

RM1999/00344/00

29-Nov-1999 Food and Drug Administration Telephone Comment/Information Request Clinical

LAM78906 23-Mar-2000 Chronology CARDS

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Application: NDA
Date Range: All 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

	Date
Conversation	Communication Type
	Document Type
CMC Labeling	Document Subtype
	Serial / Supp #

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, CMC, Labeling

	29-Nov-1999
NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Other: Status Update	29-Nov-1999 Glaxo Wellcome Telephone Conversation
ochloride) Tablets er: Status Update	General Teleconference
	Clinical Labeling Other

30-Nov-1999	
30-Nov-1999 Glaxo Wellcome Correspondence	
Amendment to Pending Application	
Labeling	

		Conversation	
Clinical	Comment/Information Request	30-Nov-1999 Food and Drug Administration Telephone	30-Nov-1999

30-Nov-1999		30-Nov-1999
30-Nov-1999 Glaxo Wellcome FAX/E-mail	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical	30-Nov-1999 Food and Drug Administration Telephone Conversation
General Memorandum	chloride) Tablets	Comment/Information Request
Labeling		Clinical

General Memorandum: Labeling

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Regulatory Affairs Chronology CARDS

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ial / Supp #

Date Range: Application: AII A

21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

23-Mar-2000 LAM78906

Document Subtype Clinical Labeling

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Safety

Comment/Information Request: Clinical, Labeling, Safety

-Dec-1999 Glaxo Wellcome Correspondence	
Amendment to Pending Application	

Clinical

Amendment to Pending Application: Clinical (Correction to previously submitted information) NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Protocol: S3BA3001

01-Dec-1999	
01-Dec-1999 Glaxo Wellcome FAX/E-mail	
General Memorandum	
Clinical	

General Memorandum: Clinical (Correction to Previously Submitted Information)

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

02-Dec-1999 Food and Drug Administration Telephone Conversation General Teleconference Other Status Update

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

General Teleconference: Other-Notification of Extension of the Review Clock, Labeling Activities, Status Update

06-Dec-1999 Glaxo Wellcome Correspondence

Amendment to Pending Application

Labeling

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Amendment to Pending Application: Labeling

23-Mar-2000 LAM78906

Regulatory Affairs Chronology CARDS

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Date Range: **Application:**

21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets	06-Dec-1999 Glaxo Wellcome FAX/E-mail	Date Communication Type
lydrochloride) Tablets	General Memorandum	Document Type
	Labeling	Document Subtype
		Serial / Supp #

06-Dec-1999 Glaxo Wellcome Correspondence

General Correspondence

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

General Correspondence: Labeling

Clinical

Response to FDA Request/Comment

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment: Clinical

07-Dec-1999

Glaxo Wellcome Correspondence

Protocol: S3B30011, S3BA3001, S3BA3002, S3BA3003

09-Dec-1999

Glaxo Wellcome Telephone Conversation

General Teleconference

Labeling Clinical

Safety Request Status Update

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Request Status Update, Safety

10-Dec-1999 Food and Drug Administration Correspondence

Acknowledgement

090-Day Review Extension

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Acknowledgement: 090-Day Review Extension

CARDS

23-Mar-2000 LAM78906 Chronology

Application: Date Range: ΑII NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Serial / Supp #

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13-Dec-1999 Date Glaxo Wellcome FAX/E-mai Communication Type Response to FDA Request/Comment Document Type Clinical Document Subtype

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment: Clinical

Protocol: S3BA2001, S3BA3001, S3BA3002, S3BP12

13-Dec-1999 Glaxo Wellcome Telephone Conversation General Teleconference Safety Request Status Update Labeling

General Teleconference: Labeling, Request Status Update, Safety NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Comment/Information Request: Clinical, Labeling NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Conversation 13-Dec-1999

Food and Drug Administration Telephone

Comment/Information Request

Clinical

Labeling

14-Dec-1999 Glaxo Wellcome Correspondence

General Correspondence

Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

General Correspondence: Clinical

Protocol: S3B20015, S3B20023, S3B30006, S3B30011, S3B30012, S3B30013, S3B30015, S3B30016, S3B30017, S3B30018, S3B30019, S3B30020, S3B30025, S3B40031, S3B40032

14-Dec-1999 Glaxo Wellcome Telephone Conversation

General Teleconference

Request Status Update Clinical Labeling

General Teleconference: Clinical, Labeling, Request Status Update

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

LAM78906

23-Mar-2000

Regulatory Affairs Chronology CARDS

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Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date Range:

Date

Communication Type

Document Type

Serial / Supp #

Document Subtype

15-Dec-1999 Glaxo Wellcome FAX/E-mail

General Memorandum

Labeling Clinical

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

General Memorandum: Clinical, Labeling

Protocol: S3B20015, S3B20023, S3B30006, S3B30011, S3B30012, S3B30013, S3B30015, S3B30016, S3B30017, S3B30018, S3B30019, S3B30020, S3B30025, S3B40031, S3B40032

15-Dec-1999 Glaxo Wellcome FAX/E-mail

General Memorandum

Clinical

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

General Memorandum: Clinical

Protocol: S3B20015, S3B20023, S3B30006, S3B30011, S3B30012, S3B30013, S3B30015, S3B30016, S3B30017, S3B30018, S3B30019, S3B30020, S3B30025, S3B40031, S3B40032

General Memorandum

15-Dec-1999 Glaxo Wellcome FAX/E-mail

Clinical

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

General Memorandum: Clinical

Protocol: S3B20015, S3B20023, S3B30006, S3B30011, S3B30012, S3B30013, S3B30015, S3B30016, S3B30017, S3B30018, S3B30019, S3B30020, S3B30025, S3B40031, S3B40032

16-Dec-1999 Glaxo Wellcome Telephone Conversation

General Teleconference

Labeling

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

General Teleconference: Labeling

16-Dec-1999 Glaxo Wellcome Telephone Conversation

General Teleconference

Labeling

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

General Teleconference: Labeling

Chronology CARDS

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Application: NDA
Date Range: All 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

23-Mar-2000 LAM78906

Date Communication Type Document Type Document Subtype Serial / Supp #

				17-Dec-1999
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets	_		Conversation	17-Dec-1999 Food and Drug Administration Telephone
rochloride) Tablets				Comment/Information Request
	Safety	Other	Labeling	Clinical

Comment/Information Request: Clinical, Labeling, Other, Safety

	17-Dec-1999
Conversation	17-Dec-1999 Food and Drug Administration Telephone
	General Teleconference
	Status Update

	20-Dec-1999
Conversation	20-Dec-1999 Food and Drug Administration Telephone
	General Teleconference
	Status Update

General Teleconference: Status Update: NDA Review, Labeling, Post Marketing Study Request	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets	Conversation

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Phase IV Commitments

21-Dec-1999

Food and Drug Administration Correspondence

Comment/Information Request

Clinical Efficacy Other Safety

CARDS

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23-Mar-2000 LAM78906 Chronology

Application: NDA
Date Range: All 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

	Date	
Conversation	Communication Type	
	Document Type	
Other	Document Subtype	
	Serial / Supp #	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Comment/Information Request: Clinical, Other: Status Update (Post- Marketing Commitment Request)

		22-Dec-1999	
		22-Dec-1999 Glaxo Wellcome Correspondence	
		Response to FDA Request/Comment	
Other	Nonclinical	Clinical	

Response to FDA Request/Comment: Commitment to Conduct Studies Post Approval NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Protocol: S3B20023 23-Dec-1999 Glaxo Wellcome FAX/E-mail

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment Nonclinical Clinical

Response to FDA Request/Comment: Commitment to conduct Phase 4 Studies

Protocol: S3B20023

23-Dec-1999 Food and Drug Administration Telephone Conversation Comment/Information Request Other Nonclinical Microbiology Clinical

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Nonclinical, Other: Post-Marketing Commitments

05-Jan-2000 Food and Drug Administration Telephone Conversation

General Teleconference

CARDS Chronology

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Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets LAM78906 23-Mar-2000

Date Range: Date ΑII General Teleconference: Status Update - Response to Proposed Labeling and Post Marketing Commitments Communication Type NDA 21-107; LOTRONEX^{IM} (Alosetron Hydrochloride) Tablets Document Type Document Subtype Serial / Supp #

07-Jan-2000 Food and Drug Administration FAX/E-mail Comment/Information Request Labeling

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Labeling

07-Jan-2000 Glaxo Wellcome Telephone Conversation NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Labeling, Other: Post-Marketing Commitments General Teleconference Other Labeling

07-Jan-2000 Food and Drug Administration Telephone Conversation Comment/Information Request Labeling

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Labeling

07-Jan-2000 Glaxo Wellcome Telephone Conversation General Teleconference Other Labeling

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Labeling, Postmarketing Commitments

10-Jan-2000 Glaxo Wellcome Telephone Conversation General Teleconference CMC Labeling

23-Mar-2000 LAM78906

Regulatory Affairs

Chronology CARDS

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Application: NDA
Date Range: All 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

v.	Document Subtype	Document Type	Communication Type	Date

General Teleconference: CMC, Labeling, Other: Post Marketing Studies NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

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	12-Jan-2000
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical (Pediatric), Labeling, Other	12-Jan-2000 Food and Drug Administration Telephone Conversation
chloride) Tablets ric), Labeling, Other	Comment/Information Request
	Clinical Labeling Other

Labeling Safety			
Clinical	Response to FDA Request/Comment	Glaxo Wellcome Telephone Conversation	13-Jan-2000
	rochloride) Tablets to FDA Labeling Recommendations	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Proposal for Revised Draft Labeling/Response to FDA Labeling Recommendations	
Labeling	General Correspondence	Glaxo Wellcome Correspondence	13-Jan-2000
	atric), Labeling, Other	Comment/Information Request: Clinical (Pediatric), Labeling, Other	
	rochloride) Tablets	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets	
Other			
Labeling		Conversation	
Clinical	Comment/Information Request	Food and Drug Administration Telephone	12-Jan-2000

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical, Labeling, Safety

LAM78906 23-Mar-2000

Regulatory Affairs

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Application: NDA
Date Range: All 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date	Communication Type	Document Type	Document Subtype Seri	Serial / Supp #
13-Jan-2000	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical	loride) Tablets		
13-Jan-2000	Glaxo Wellcome FAX/E-mail	General Memorandum	Labeling	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Memorandum: Labeling	loride) Tablets		
14-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Labeling Request Status Update Safety	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Request Status Update (NDA Review), Safety	loride) Tablets st Status Update (NDA Review), Safety		
17-Jan-2000	Glaxo Wellcome Correspondence	Special Safety Update	The second of th	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Safety Update Response to FDA Request/Comment (Final Report for Study S3BA3003)	loride) Tablets for Study S3BA3003)		
Protocol: S3BA3003	003			
18-Jan-2000	Food and Drug Administration Correspondence	Comment/Information Request	Clinical	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Additional Phase IV Commitments

LAM78906 23-Mar-2000

Regulatory Affairs CARDS Chronology

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Application: NDA 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
18-Jan-2000	Food and Drug Administration Correspondence	Comment/Information Request	Clinical	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Commitment to Post-Approval Studies	ıloride) Tablets ost-Approval Studies		
18-Jan-2000	Food and Drug Administration Telephone Conversation	Comment/Information Request	CMC	
	NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: CMC	ıloride) Tablets		
19-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	BA/BE CMC Labeling Other	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: NDA Review Status Update: BA/BE, CMC, Labeling, Other	nloride) Tablets ate: BA/BE, CMC, Labeling, Other		
Protocol: S3BA3003	003			
20-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Other	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: NDA Review Status Update	ıloride) Tablets ate		
21-Jan-2000	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical CMC Nonclinical	

23-Mar-2000

Regulatory Affairs CARDS

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Chronology

21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Application: NDA
Date Range: All

	Date	
	Communication Type	
	Document Type	
Other	Document Subtype	
	Serial / Supp #	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Response to FDA Request: Commitment to Conduct Studies Post Approval; Agreement to Change in Drug Product Specifications

				21-Jan-2000	
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets				21-Jan-2000 Glaxo Wellcome FAX/E-mail	
Hydrochloride) Tablets				General Memorandum	
	Other	Nonclinical	CMC	Clinical	

General Memorandum: Commitment to Conduct Studies Post Approval.

	27-Jan-2000		27-Jan-2000
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Request Status Update	27-Jan-2000 Glaxo Wellcome Telephone Conversation	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Request Status Update	27-Jan-2000 Glaxo Wellcome Telephone Conversation
chloride) Tablets	General Teleconference	chloride) Tablets	General Teleconference
	Request Status Update		Request Status Update

LAM78906 23-Mar-2000

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Chronology

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Application:NDA21107; LOTRONEX™ (Alosetron Hydrochloride) TabletsDate Range:All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
28-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Labeling Other	
		Response to FDA Request/Comment	Clinical Labeling	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Other: NDA Review Status	ochloride) Tablets her: NDA Review Status		
31-Jan-2000	31-Jan-2000 Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets	ochloride) Tablets		

01-Feb-2000		
01-Feb-2000 Glaxo Wellcome FAX/E-mail	NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Labeling	
Response to FDA Request/Comment	chloride) Tablets	
Other		,

01-Feb-2000		01-Feb-2000		01-Feb-2000	
Food and Drug Administration Telephone Conversation	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Financial Disclosure Information	Glaxo Wellcome FAX/E-mail	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Other: Financial Disclosure Information	Glaxo Wellcome FAX/E-mail	
Comment/Information Request	rochloride) Tablets ıl Disclosure Information	Response to FDA Request/Comment	rochloride) Tablets inancial Disclosure Information	Response to FDA Request/Comment	
Labeling Other		Other		Other	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Comment/Information Request: Other: Financial Disclosure

LAM78906 23-Mar-2000

Regulatory Affairs

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Application: NDA
Date Range: All

21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

ommunication type	Document Lype	Document Subtype
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	03-Feb-2000		03-Feb-2000		02-Feb-2000		02-Feb-2000		02-Feb-2000
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Labeling	Glaxo Wellcome Telephone Conversation	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Labeling	Glaxo Wellcome Telephone Conversation	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Labeling	Glaxo Wellcome Telephone Conversation	NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Labeling	Food and Drug Administration Telephone Conversation	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Memorandum: Labeling	Glaxo Wellcome FAX/E-mail
ochloride) Tablets	Response to FDA Request/Comment	ochloride) Tablets	General Teleconference	ochloride) Tablets	General Teleconference	ochloride) Tablets	General Teleconference Comment/Information Request	ochloride) Tablets	General Memorandum
	Labeling		Labeling		Labeling		Other Labeling		Labeling

Regulatory Affairs CARDS Chronology

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Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Date Range: All

LAM78906 23-Mar-2000

	04-Feb-2000			04-Feb-2000	Date
NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets Comment/Information Request: Labeling	Food and Drug Administration FAX/E-mail	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: CMC, Labeling, Request Status Update		04-Feb-2000 Glaxo Wellcome Telephone Conversation	Communication Type
chloride) Tablets	Comment/Information Request	schloride) Tablets st Status Update		General Teleconference	Document Type
	Labeling		Labeling Request Status Update	СМС	Document Subtype
					Serial / Supp #

07-Feb-2000 Glaxo Wellcome FAX/E-mail General Memorandum: Labeling NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Memorandum Labeling

07-Feb-2000 Glaxo Wellcome Telephone Conversation General Teleconference Labeling

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets
General Teleconference: Labeling (Final Labeling Negotiations)

Commitment: Fax labeling with final agreed changes marked.

Commitment: Fax labeling with final agreed changes marked Commitment Responsibility: M Baumgartner Commitment Due Date: 07-Feb-2000

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NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Memorandum: Labeling

23-Mar-2000 LAM78906

Regulatory Affairs

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Application: NDA
Date Range: All 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
08-Feb-2000	08-Feb-2000 Glaxo Wellcome Telephone Conversation	General Teleconference	CMC	
			Labeling Other	
			Request Status Update	
	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: CMC, Labeling, Other (Pediatrics), Request Status Update	ochloride) Tablets (Pediatrics). Request Status Update		

08-Feb-2000 Glaxo Wellcome FAX/E-mail NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment

Clinical

Protocol: S3B10903, S3B10934, S3B30015, S3B30019

Response to FDA Request/Comment: Clinical

	09-Feb
	-2000
NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Approval Letter	09-Feb-2000 Food and Drug Administration Correspondence Approval Letter
	etter

09-Feb-2000			09-Feb-2000	
09-Feb-2000 Food and Drug Administration Correspondence	NDA 21-107; LOTRONEX TM (Alosetron Hydrochloride) Tablets General Teleconference: Other, Status Update: Labeling Request	Conversation	09-Feb-2000 Food and Drug Administration Telephone	
Approval Letter	hloride) Tablets beling Request		General Teleconference	
Labeling		Status Update	Other	

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Approval Letter: Labeling

23-Mar-2000

Regulatory Affairs Chronology CARDS

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21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date Range: Application: NDA

Date

Communication Type

Document Type

Document Subtype

Serial / Supp #

10-Feb-2000 Glaxo Wellcome Correspondence

Special Supplement: Changes Being Effected

CMC

SUPAC IR: Special Supplement: Changes Being Effected in 30 Days NDA 21-107; LOTRONEXTM (alosetron hydrochloride) Tablets

Qualification of an Alternate Primary Packaging Site

10-Feb-2000 Glaxo Wellcome Telephone Conversation

General Teleconference

CMC

NDA 21-107; LOTRONEXTM (alosetron hydrochloride) Tablets

General Teleconference: CMC

Commitment: Submit CBE-30

Commitment Responsibility: A Mitchell

Commitment Due Date: 10-Feb-2000

10-Feb-2000 Glaxo Wellcome Correspondence

General Correspondence

CMC Field Copy

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

General Correspondence: CMC Field Copy

22-Feb-2000

Conversation Food and Drug Administration Telephone

General Teleconference

Status Update

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

General Teleconference: Status Update Concerning CBE-30

23-Feb-2000 Glaxo Wellcome FAX/E-mail

General Memorandum

Other

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

CARDS

23-Mar-2000 LAM78906 Chronology

10:04:33

Application: Date Range: All A 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Date Communication Type General Memorandum: Other Document Type Document Subtype Serial / Supp #

23-Feb-2000 Glaxo Wellcome Telephone Conversation General Teleconference

Labeling Clinical

Other

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

General Teleconference: Clinical, Labeling, Other: Pediatrics

Protocol: S3BA3003

25-Feb-2000 Glaxo Wellcome Correspondence 015-Day ADR Report

Initial

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

015-Day ADR Report: Initial

ADR: A0108355A

Food and Drug Administration Telephone General Teleconference Status Update

Conversation

28-Feb-2000

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

General Teleconference: Status Update; Notification that CBE-30 submitted February 10, 2000 is approved

02-Mar-2000 Glaxo Wellcome FAX/E-mail General Memorandum

Labeling

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets

General Memorandum: Labeling

02-Mar-2000 Food and Drug Administration Telephone Conversation

General Teleconference

Status Update

Other

23-Mar-2000

Regulatory Affairs CARDS

Chronology

55 10:04:33

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Date Range: ΑII

Date

Communication Type Document Type

Document Subtype

Serial / Supp #

NDA 21-107; LOTRONEX^{IM} (Alosetron Hydrochloride) Tablets

General Teleconference: Other

Protocol: S3BA3003

06-Mar-2000 Glaxo Wellcome FAX/E-mail

General Memorandum

Other

Request Status Update

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Other - Return of Pathology Slides

06-Mar-2000 Glaxo Wellcome Correspondence

Response to FDA Request/Comment

Clinical Efficacy Other

Safety

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Response to FDA Request/Comment: Clinical

Protocol: S3BA3001, S3BA3002, S3BA3003

07-Mar-2000 Food and Drug Administration Correspondence

Approval Letter

001

NDA 21-107/S-001; LOTRONEXTM (Alosetron Hydrochloride) Tablets

Approval Letter

13-Mar-2000 Glaxo Wellcome Telephone Conversation

Response to FDA Request/Comment

Response to FDA Request/Comment NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

14-Mar-2000 Glaxo Wellcome Correspondence

General Correspondence

Labeling

CARDS

Chronology

56 10:04:33

Application: NDA
Date Range: All 21107; LOTRONEXTM (Alosetron Hydrochloride) Tablets LAM78906 23-Mar-2000

Communication Type Document Type

Document Subtype

Serial / Supp #

General Correspondence: Final Printed Labeling (FPL) for approved NDA 21-107. NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Conver	16-Mar-2000 Food a
onversation	16-Mar-2000 Food and Drug Administration Telephone
	General Teleconference
Status U _I	Other

NDA 21-107; LOTRONEXTM (Alosetron Hydrochloride) Tablets General Teleconference: Status Update: Pediatric Request, Labeling, Clinical Data

22-Mar-2000 Glaxo Wellcome Correspondence 15-day Initial Postmarketing Reports 015-Day ADR Report

Initial

Update

_	EXHIBIT 9G
	Document Chronology / Due Diligence Logs for
	IND No. 59,496

Chronology

1 10:19:02

Application:

59496; Alosetron Hydrochloride Oral Solution

Date Range:

23-Mar-2000 LAM78906

	17-Dec-1999	Date	
	17-Dec-1999 Glaxo Wellcome Correspondence	Communication Type	
	Initial Investigational New Drug Application	Document Type	
Protocol(s) Included	CMC	Document Subtype	-
	0000	Serial / Supp #	

Study Reports

IND; Alosetron Hydrochloride Oral Solution

Initial Investigational New Drug Application: CMC, Protocol(s) Included

Serial No.: 0000

Protocol with Investigator(s):

S3B10903 with:

Gregory L Kearns, Pharm.D. Protocol with Report(s):

S3B10903 with:

NN1999/00069/00

	20-Dec
	-1999
IND; Alosetron Hydrochloride Oral Solution	20-Dec-1999 Glaxo Wellcome FAX/E-mail
	General Memorandum
	Other

General Memorandum: Other

	Conversation	3-Dec-1999 Food and
	ation	23-Dec-1999 Food and Drug Administration Telephone
-		General Teleconference
	Other	IND # Assigned

IND 59,496; Alosetron Hydrochloride Oral Solution

General Teleconference: IND # Assigned, Other: Waiver for 30-day wait granted

0001	Initial	10-Day ADR Report	07-Jan-2000 Glaxo Wellcome Correspondence	07-Jan-2000
			903	Protocol: S3B10903

IND 59,496; Alosetron Hydrochloride Oral Solution

Serial No.: 0001 10-Day ADR Report: Initial

Protocol: S3B30012

CARDS

Regulatory Affairs

.23-Mar-2000 59496; Alosetron Hydrochloride Oral Solution Chronology 2 10:19:02

Date Range: Application:

Date

Communication Type

ADR: A010/932A

Document Type

11-Jan-2000 Glaxo Wellcome Correspondence

10-Day ADR Report

Document Subtype

Serial / Supp #

0002

Initial

IND 59,496; Alosetron Hydrochloride Oral Solution Serial No.: 0161

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0002

10-Day ADR Report: Initial

Protocol: S3B30011 ADR: A0108355A

13-Jan-2000 Food and Drug Administration Correspondence Acknowledgement IND # Assigned

IND 59,496; Alosetron Hydrochloride Oral Solution

Acknowledgement: IND # Assigned

03-Feb-2000 Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report Initial 0003

Serial No.: 0164

Serial No.: 0003 IND 59,496; Alosetron Hydrochloride Oral Solution

10-Day ADR Report: Initial

ADR: B0070503A Protocol: S3BB3002

21-Feb-2000 Glaxo Wellcome Correspondence Protocol Amendment: New Investigator Amendment: Other Change in Medical Monitor Investigator Add 0004

Protocol Amendment: New Investigator Amendment: Other, Change in Medical Monitor IND 59,496; Alosetron Hydrochloride Oral Solution

Serial No.: 0004

Chronology **CARDS**

10:19:02

Application: ₽IJ 59496; Alosetron Hydrochloride Oral Solution

Date Range:

23-Mar-2000

LAM7§906

Date Communication Type Document Type Document Subtype Serial / Supp #

Protocol: S3B10903

Protocol with Investigator(s):

S3B10903 with:

Jeffrey L Blumer, M.D., B. Ulysses Kwang Li, M.D.

Comment: William Forbes Brodie-Brown, M.B., CH.B

24-Feb-2000 Glaxo Wellcome Correspondence 10-Day ADR Report Follow-up 0005

Serial No.: 0167 IND 59,496; Alosetron Hydrochloride Oral Solution

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0005

10-Day ADR Report: Follow-up

ADR: A0108355A Protocol: S3B30011

21-Mar-2000 Glaxo Wellcome Correspondence

10-Day ADR Report

Initial

9000

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0174

IND 59,496; Alosetron Hydrochloride Oral Solution

Serial No.: 0006

10-Day ADR Report: Initial

ADR: A0114615A Protocol: S3B20023

22-Mar-2000 Glaxo Wellcome Correspondence

10-Day ADR Report

Follow-up

0007

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Serial No.: 0176

IND 59,496; Alosetron Hydrochloride Oral Solution

Serial No.: 0007

10-Day ADR Report: Follow-up

Protocol: S3B30011

Regulatory Affairs CARDS Chronology

4 10:19:02

59496; Alosetron Hydrochloride Oral Solution

Application: IND Date Range: All

LAM78906 23-Mar-2000

Date Communication Type ADR: A010/106A Document Type **Document Subtype**

Serial / Supp #

EXHIBIT 10

Patent Term Extension Calculations for Patent Term Extension of U.S. Patent No. 5,360,800

Express Mail Label No. EM484297842US

Patent Term Extension Calculation for U.S. Patent No. 5,360,800

٠	P	a	ten	t	Issu	e	D	at	e:
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1 Nov 1994

IND Effective Date of 34,672: 10 May 1990
IND Effective Date of 39,083: 11 April 1992
IND Effective Date of 45,128: 25 May 1994
Period of Testing Phase:

1 Nov 94 – 31 Dec 94 = 61

1 Nov 94 – 31 Dec 94	=	61
1 Jan 95 – 31 Dec 95	=	365
1 Jan 96 – 31 Dec 96	=	366
1 Jan 97 – 31 Dec 97	=	365
1 Jan 98 – 31 Dec 98	=	365
1 Jan 99 – 29 Jun 99	=	180
		1702 days

IND Phase /2 = 1702/2 = 851 days

NDA Submission Date:

30 Jun 1999

NDA Approval Date:

9 Feb 2000

Period of Approval Phase:

		225 days
1 Feb 00 - 9 Feb 00	=	_9
1 Jan 00 - 31 Jan 00	=	31
1 Dec 99 – 31 Dec 99	=	31
1 Nov 99 – 30 Nov 99	=	30
1 Oct 99 – 31 Oct 99	=	31
1 Sep 99 – 30 Sep 99	=	30
1 Aug 99 – 31 Aug 99	=	31
1 Jul 99 – 31 Jul 99	=	31
30 Jun 99	=	1

IND phase/2 + NDA phase = 851+225 = 1076

Total Patent Term Extension: 1076 days

Patent Expiry by Terminal Disclaimer:

2 Feb 2010

Extended Expiry:

Expiration + 1076-Day Patent

Term Extension: 13 Jan 2013

14 Year Cap from NDA Approval Date:

NDA Approval Date + 14 yrs=

9 Feb 00 + 14 yrs = 9 Feb 2014

14 year Patent Term Cap does not apply.